CECIL TEXTBOOK of MEDICINE

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198 PRINCIPLES OF CANCER THERAPY

Joseph R. Bertino ■ *Sydney E. Salmon*

The development of effective anticancer drugs has progressively integrated medical management with surgery and radiation therapy in the multimodal treatment of cancer. The development of new cytotoxic and endocrine agents and the introduction of biologic therapy based on recombinant synthesis of interferons and cytokines have expanded medical management, as has the treatment of the complications of cancer. The physician also must be familiar with palliative aspects of cancer care, including management of pain (see Chapter 27) and treatment of life-threatening complications (see Chapter 199).

Although current systemic therapy can cure few forms of metastatic cancer, it is now increasingly effective as a component of multimodal management of apparently localized cancers known to have a high frequency of occult micrometastatic spread. This approach is predicated on the availability of specific systemic agents with antitumor activity in advanced cancers of the same histopathology. Not all patients are candidates for attempts at cancer therapy because of limitations in available drugs or co-morbidity from other medical problems. To a significant extent, cancer is a disease of the elderly, and treatment for many types of cancer in patients older than the age of 65 remains difficult because of the reduced host tolerance to the toxicities of many cancer chemotherapeutic agents. Patients and families must be fully informed about the nature of planned treatment, whether curative or palliative in intent. Inasmuch as prognosis for individual patients is currently based on statistical estimates, the physician must evaluate each patient individually in relation to relevant prognostic factors in attempting to develop a treatment plan.

DEVELOPMENT OF A TREATMENT PLAN

The major clinical features of cancer to be considered in developing a treatment plan include (1) specific histologic diagnosis of the neoplasm, (2) tumor burden and extent of specific organ involvement (stage), and (3) biologic characteristics and other prognostic factors relevant to the specific type of cancer.

DIAGNOSIS. Accurate histologic diagnosis and staging critically influence treatment selection. Increasingly, immunohistochemical analysis helps in subtyping lymphomas and distinguishing among various morphologically "undifferentiated" neoplasms (see Chapter 200). Tumors of diverse histogenesis can have markedly different prognosis and treatment. Electron microscopy sometimes can help by identifying specific morphologic features such as melanosomes (in melanoma) or desmosomes (in carcinomas) that permit more specific classification. Other distinctive biologic markers include immunohistochemistry (e.g., overexpression of cyclin D in mantle cell lymphoma), hormone receptor expression, serum or urinary tumor markers (e.g., β-human chorionic gonadotropin, α-fetoprotein, carcinoembryonic antigen, CA-125, myeloma proteins, urinary 5-hydroxyindole acetic acid), karyotype, or molecular analysis. Increasingly, molecular biologic methods for DNA analysis are also playing a role in diagnosis by identifying characteristic gene rearrangements (e.g., Southern blots), gene deletions, or oncogene expression. Cellular proto-oncogene amplification and expression have been linked to the pathogenesis of various neoplasms (see Chapter 191). Recently identified genes regulate the cell cycle and provide "checkpoints" when damage to DNA occurs. Determination of the status of the products of the *p53* and retinoblastoma genes is becoming increasingly important in assessing tumor biology and prognosis, because tumors with mutant or null *p53* and lacking a functional retinoblastoma protein may have a poor prognosis.

In the leukemias and lymphomas, such information can prove important for selecting appropriate treatment approaches. For example, the approach to treatment of T-cell or B-cell lymphomas differs as a function of cell lineage, which often cannot be identified with standard histologic approaches. Specialized studies can in some instances provide evidence for a treatable or curable form of cancer that might otherwise go unrecognized.

STAGING. Assessment of the body burden and spread of cancer by clinical means (staging) is important in developing the treatment plan. Most staging systems assess the size of the primary tumor and define regional lymph node involvement as well as the presence or absence of distant metastatic disease. It is important to distinguish between clinical and pathologic staging and to recognize that pathologic staging employing surgical biopsy is generally more accurate. Increasingly, staging can be accomplished by using non-invasive imaging procedures such as chest radiography and magnetic resonance imaging (MRI) or computed tomography (CT). In the diagnostic evaluation of specific forms of cancer, such as breast or prostate cancer, bone scans can be useful to evaluate advanced disease but have minimal use in early localized disease unless the patient has skeletal symptoms. For multiple myeloma, bone scans are of less use than skeletal radiographs. The temptation to use a variety of redundant and expensive tests such as CT, MRI, and ultrasonography to examine the same site should be avoided. It is important to focus on the benefit-to-risk ratio of invasive procedures such as staging laparotomy. The patient's age, performance status, concomitant medical problems, and histologic diagnosis all must be considered; then the procedure should be performed only if it may influence the treatment plan. For patients who present with life-threatening local complications of cancer (e.g., spinal cord compression, upper airway obstruction, the superior vena cava syndrome, or obstructive jaundice) (see Chapter 199), it is usually necessary first to treat the local complication. Even in these cases, a pathologic diagnosis should be established if at all possible before treatment is started.

OVERALL ASSESSMENT. Once diagnosis and staging have been performed, the information must be integrated into an optimal treatment plan. For patients with apparently localized cancers, multidisciplinary input is important, because a combined-modality approach may be indicated. The biologic characteristics of the specific cancer must be considered. For many tumor types, histopathologic features such as grade of tumor cell differentiation are important, with a less differentiated or undifferentiated phenotype indicating a more aggressive neoplasm. For some sites, other biologic factors are of greater value than histologic grade. For example, in breast cancer, the presence or absence of estrogen or progesterone receptors and the DNA-index and ploidy status as determined by flow cytometry provide useful information in developing a treatment plan. Some patients with a minimal tumor burden (e.g., stage I) of currently incurable B-cell neoplasms (e.g., chronic lymphocytic leukemia [CLL] and multiple myeloma) are best watched expectantly rather than treated. By contrast, almost all patients with diffuse large cell (intermediate- or high-grade) lymphoma should be treated aggressively with curative intent, irrespective of stage, unless they are very elderly and have other major medical problems.

In any given patient, it is important to decide whether curative therapy is available or not, and, if so, whether the patient's age and overall medical condition permit a curative approach. If cure is not an option, one must consider whether palliation with prolongation of survival (and relief of symptoms) can be achieved. For old and infirm patients, a palliative approach may be preferable, particularly if there is significant morbidity associated with the treatment approach under consideration. On the other hand, some forms of cancer therapy are very effective and well tolerated even with advanced age (e.g., use of tamoxifen in adjuvant therapy of postmenopausal breast cancer or of chlorambucil for chronic lymphocytic leukemia). For many tumor types, it is important to examine results of recent prospective clinical trials relevant to the patient's diagnosis and clinical setting and, if possible, to enter patients in clinical trials.

THERAPEUTIC MODALITIES

Three primary therapeutic approaches dominate the treatment of cancer: surgery, radiation therapy, and medical therapy. A fourth modality, biologic therapy (cytokines, antibodies, vaccines), is beginning to add another dimension to treatment programs.

Surgery

Cancer surgery is most useful to establish a tissue diagnosis, to excise the primary tumor with clear surgical margins free of tumor, and to determine the extent of cancer with staging procedures. Surgery is a simple and safe means to remove solid tumors when the tumor is confined to a specific anatomic site of origin. However, in the case of some solid tumors, most patients already have metastatic disease at the time of presentation. In evaluating major surgery for an individual patient, it is important to assess the operative risk-to-benefit ratio for the procedure in the context of the patient's general health status, the extent of the tumor, and the likelihood that it can be completely removed. Additionally, the technical complexity of the surgical procedure, the type of anesthesia needed, and the experience of the personnel must also be considered.

With advances in both radiation and chemotherapy, the need for radical surgery has diminished. However, it remains a major primary approach to curative cancer therapy. For testicular cancer, even in the presence of limited metastatic disease, regional lymphadenectomy after radical orchiectomy can be curative and eliminate the need for chemotherapy in some patients who have metastases only to retroperitoneal lymph nodes. For many other sites, surgical resection of regional lymph nodes is performed for diagnostic rather than therapeutic purposes. For example, in breast cancer, the presence or absence of axillary lymph node involvement is the single most important factor in evaluating the likelihood of distant recurrence, and this information is currently not obtainable by non-surgical means. Similarly, surgical staging of rectal involvement in colorectal cancer plays an important role in deciding whether adjuvant systemic chemotherapy is indicated.

Initial cancer therapy often requires a multimodal approach to maximize the chance of cure while simultaneously reducing the extent of surgery required. Multimodal approaches require close communication among the involved physicians before surgery. Early communication is improved by obtaining histopathologic diagnosis by needle biopsy or local excision of the primary cancer before more extensive therapy. Two examples are of note in this regard: (1) the management of osteogenic sarcoma with limb salvage surgery, irradiation, and adjuvant chemotherapy and (2) the management of early breast cancer with lumpectomy, axillary staging followed by primary irradiation, and adjuvant systemic administration of cytotoxic or endocrine agents. In both instances, the combined approach yields a better cosmetic and functional outcome. Screening mammography can establish a diagnosis of breast cancer when the tumor is less extensive and when likelihood of cure is greater. Improved plastic surgical techniques have also made breast reconstruction possible for women who either require or prefer mastectomy rather than lumpectomy followed by radiation therapy.

In addition to its use in diagnosis, staging, and primary therapy, cancer surgery also plays an important role in the management of some patients with more extensive cancer. In ovarian cancer, when the gynecologic oncologist "debulks" peritoneal and omental spread and leaves the patient with minimal residual disease, patients become better candidates for systemic chemotherapy and have a better survival. Additionally, early resection of pulmonary metastases of soft tissue sarcomas or of solitary brain metastases in melanoma, colon, or breast cancer may provide marked palliation and improved survival, albeit with only occasional cures.

Radiation Therapy

Radiation therapy has made major strides in instrumentation, physics, radiobiology, treatment planning, and applications to curative and palliative cancer therapy. In general, the term *radiation* refers to ionizing radiation that is either electromagnetic or particulate (e.g., x-rays). Compared with surgery, radiation therapy has distinct advantages in the locoregional treatment of cancer. Radiation causes less acute morbidity and can be curative for some specific sites while preserving organ or tissue structure and function. An example is the use of radiation for the curative treatment of early-stage laryngeal cancer wherein vocal function can be preserved.

The basic unit of ionizing irradiation is the gray (Gy), which has superseded the rad (1 Gy = 100 rads = 100 cGy) (see Chapter 19). By interaction with molecular oxygen, radiation induces the formation of superoxide, hydrogen peroxide, or hydroxyl radicals that damage or break cellular DNA, the critical target for radiation-induced cell death. Both single- and double-strand breaks of the DNA helix can be induced, with the latter constituting lethal damage. Single-strand breaks, if not repaired by the cell, can also result in cell death. High linear energy transfer (LET) radiation can induce direct damage to the molecular structure of DNA.

Radiation has limitations in the treatment of bulky tumors. Large tumors frequently have poorly perfused, hypoxic zones in which radiation often fails to induce needed reactive intermediaries. Various forms of irradiation are used for different therapeutic objectives. For example, electron-beam irradiation deposits most of its energy in the skin and soft tissues and can be useful for superficial therapy of skin neoplasms such as mycosis fungoides. Low-energy (kilovoltage) x-rays expend most of their effects on the overlying tissues above a deep-seated tumor and therefore cause considerable normal tissue damage. By contrast, higher-energy x-rays (megavoltage) or x-irradiation from a cobalt-60 source spare the skin, deposit their energy at greater depth, and provide a better approach to treating deep-seated neoplasms. Use of radioactive implants also can be useful in some settings (e.g., cervical cancer, prostate cancer). The use of multiple irradiation fields reduces the dose to normal tissue while increasing the dose to the tumor. The use of fractionated doses causes less cumulative damage to normal tissues than to the tumor, because the normal tissues are often able to repair sublethal damage more quickly. Additionally, as a tumor shrinks with therapy, its oxygenation can improve and render it more radiosensitive. The selection of treatment is based on the relative radiosensitivity of the tumor and of the normal organs and tissues within the radiation field (Table 198–1).

The combined use of multiple fields, fractionated irradiation, and megavoltage radiation equipment is optimized by treatment individualized to the patient's tumor. Although the major uses of radiation therapy involve local irradiation of sites of tumor involvement, total-body irradiation or total lymphoid irradiation is a valuable part of a preparative regimen for allogeneic or autologous bone marrow transplantation for leukemia or lymphoma (see Chapter 182).

Radiation therapy has important palliative applications. One of these is for bone pain due to metastatic involvement of the skeleton. Irradiation can also cause sufficient cytoreduction of tumor in bone to permit healing of osteolytic lesions and thereby prevent pathologic fractures of weight-bearing bones. Other examples include tumor shrinkage to relieve postobstructive infection in lung cancer and to suppress bronchial or gastric bleeding secondary to cancer.

Although modern radiation therapy with megavoltage equipment has proved to be extremely useful, even higher energy radiation approaches are currently in development. These include the use of higher LET sources of irradiation (e.g., neutrons, charged particles, heavy ions), which may also provide selective advantages for specific tumor sites and reduce the need for oxygenation of tumor tissue. Additionally, several classes of compounds are under study as radiosensitizers to enhance the cytotoxic effects of radiation on tumor cells. One class is the halopyrimidines, including bromodeoxyuridine, fluorouracil, and fluorodeoxyuridine, which sensitize

Table 198–1 ■ TOLERANCE OF NORMAL TISSUES TO IRRADIATION

TISSUE	TOXIC EFFECT	LIMITING DOSE (Gy)*
Bone marrow	Aplasia	2.5
Lung	Pneumonitis, fibrosis	15.0
Kidney	Nephrosclerosis	20.0
Liver	Hepatitis	25.0
Spinal cord	Infarction, necrosis	45.0
Intestine	Ulceration, fibrosis	45.0
Heart	Pericarditis, myocarditis	45.0
Brain	Infarction, necrosis	50.0
Skin	Dermatitis, sclerosis	55.0

*Radiation in 2.0-Gy fractions to the whole organ for 5 days weekly produces a 5% incidence of the listed toxicities at the limiting doses listed.

DNA to strand breakage by radiation. Other chemotherapeutic agents, including gemcitabine and taxol, are also under investigation as radiosensitizing agents. Several sulfhydryl compounds (e.g., amifostine) are also under investigation as potential radioprotective agents.

Although the term *radiation* normally refers to ionizing irradiation, several other forms of radiation are also used in cancer treatment. These include hyperthermia and photodynamic therapy, both of which are still undergoing development. Some tumors show thermal sensitivity to temperatures in the range of 41° to 43° C and may be more sensitive than surrounding normal tissues. Hyperthermia appears to work best on bulky tumors with poor blood supply in which the tumor cells are in an acidic environment. A variety of approaches can induce local or regional hyperthermia (e.g., ultrasonography, microwaves, regional perfusion) and may enhance the effects of ionizing irradiation or chemotherapy on local tumors.

Photodynamic therapy (PDT) involves the preliminary systemic administration of a photosensitizing compound such as a hematoporphyrin derivative (e.g., dihematoporphyrin ether, Photofrin II). Such hematoporphyrins are concentrated in the vicinity of local tumors and can be activated with local exposure to visible red light (usually 630 nm), with a resulting preferential toxicity to cancer cells. The intense light used for PDT can be delivered by means of a fiberoptic probe, which can be used for various internal sites as well as on the skin. The mechanism of action of PDT is poorly understood but may involve vascular damage or a direct toxic effect on tumor cells. Side effects of photodynamic therapy include hypersensitivity to light (skin and eyes). Locally, PDT induces transient sunburn and hyperpigmentation as well as local tumor necrosis. Tumor sites amenable to PDT include skin recurrences of breast cancer (e.g., chest wall) and malignant lesions in the endobronchus, peritoneal cavity, and bladder. Photodynamic therapy has not been approved by the U.S. Food and Drug Administration (FDA) and remains investigational.

Medical Therapy

Curative therapy has been developed for a series of relatively uncommon disseminated neoplasms, and useful palliative therapy has been developed for some common forms of cancer (Table 198–2). With rare exceptions, effective therapy has used combinations of anticancer drugs. Increasingly, anticancer drugs are used in concert with surgery and/or irradiation.

Ideally, anticancer drugs should eradicate cancer without harming normal tissues; however, this goal has not been achieved, and most useful drugs have significant side effects. The introduction of anticancer drugs for clinical use has largely been predicted from animal tumor models. Perhaps because the initial murine models were for acute leukemia, many of the developed drugs are general antiproliferative agents. Accordingly, they are more effective against rapidly proliferating tumors than against some of the more slowly growing solid tumors and are more toxic to rapidly growing tumors than to normal host tissues. Nevertheless, such generally antiproliferative agents can have important toxic side effects on normal tissues that divide rapidly, such as bone marrow, gastrointestinal mucosa, and skin.

Table 198–2 ■ RESPONSIVENESS OF CANCER TO CHEMOTHERAPY

Cure (>30%) of Advanced Disease
Choriocarcinoma
Acute lymphocytic leukemia (childhood)
Malignant lymphoma (Hodgkin's disease, diffuse high-grade or intermediate-grade non-Hodgkin's lymphoma)
Hairy cell leukemia
Testicular cancer
Childhood solid tumors (embryonal rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumor)
Acute myelocytic leukemia
Acute lymphocytic leukemia (adult)
Promyelocytic leukemia
Significant Palliation, Some Cures of Advanced Disease (5–30%)
Ovarian cancer
Bladder cancer
Small cell lung cancer
Gastric cancer
Palliation, Probably Increases Survival
Breast cancer
Multiple myeloma
Head and neck cancer
Adjuvant Treatment Leading to Increased Cure
Breast cancer
Colon cancer
Osteogenic sarcoma
Early-stage large cell lymphoma

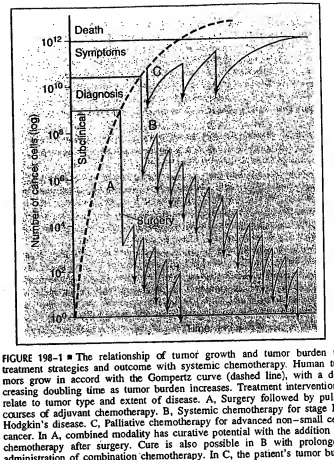

FIGURE 198–1 ■ The relationship of tumor growth and tumor burden to treatment strategies and outcome with systemic chemotherapy. Human tumors grow in accord with the Gompertz curve (dashed line), with a decreasing doubling time as tumor burden increases. Treatment interventions relate to tumor type and extent of disease. A, Surgery followed by pulse courses of adjuvant chemotherapy. B, Systemic chemotherapy for stage III Hodgkin's disease. C, Palliative chemotherapy for advanced non–small cell cancer. In A, combined modality has curative potential with the addition of chemotherapy after surgery. Cure is also possible in B with prolonged administration of combination chemotherapy. In C, the patient's tumor burden is too great and the potency of the drugs for this specific form of cancer is inadequate because of development of drug resistance. (Modified from Salmon SE, Sartorelli AC: Cancer chemotherapy. *In* Katzung BG [ed]: Basic and Clinical Pharmacology, 4th ed. Norwalk, CT, Appleton & Lange, 1989, p 685.)

CELL KINETICS AND RESPONSE TO CHEMOTHERAPY. A number of related factors, including total tumor burden, cell kinetics, and intrinsic sensitivity, influence the response to anticancer drugs. In both animal models and human tumors, growth occurs in accord with gompertzian kinetics. Initially, growth occurs rapidly, and most tumor cells traverse the complete cell cycle. As the tumor burden grows larger, the rate of tumor cell doubling progressively slows (Fig. 198–1), and the fraction of cells traversing the cell cycle decreases as more and more cells remain "hung up" in a G_0 phase. Whereas the population doubling time may be in the range of 1 to 2 days at the subclinical phase (with less than 1 g of tumor), by the time the tumor burden has reached 1 kg or more, the tumor cell population doubling time may be 3 to 6 months. A significant problem in the treatment of high tumor burden metastatic solid tumors is that the tumor exhibits a significant degree of heterogeneity; subpopulations of cells exhibit differing biologic, kinetic, antigenic, and drug-sensitivity profiles.

Several important features related to cell kinetics and tumor burden are important with respect to drug dose, scheduling, and response to chemotherapy. Anticancer drugs can be classified as either cell cycle specific (CCS) or cell cycle non-specific (CCNS) (Table 198–3). CCNS agents have greater effects on cycling than on non-cycling cells but nonetheless can exert anticancer effects on non-cycling cells, whereas CCS agents do not. Endocrine agents

Table 198–3 ■ RELATIONSHIP OF TUMOR CELL CYCLE TO ACTIVITY OF MAJOR CLASSES OF CYTOTOXIC ANTICANCER DRUGS

CELL CYCLE–SPECIFIC (CCS) AGENTS	CELL CYCLE–NON-SPECIFIC (CCNS) AGENTS
Antimetabolites (cytarabine, fluorouracil, methotrexate, mercaptopurine, hydroxyurea)	Alkylating agents (busulfan, cyclophosphamide, mechlorethamine, melphalan, thiotepa, chlorambucil)
Anthracyclines (doxorubicin, daunorubicin)	Antibiotics (dactinomycin, mitomycin)
Bleomycin	Platinum compounds (cisplatin, carboplatin)
Camptothecins (irinotecan, topotecan)	Nitrosoureas (BCNU, CCNU)
Plant alkaloids (vincristine, vinblastine, etoposide, taxol)	Dacarbazine
	L-Asparaginase

are also in a sense cycle active, because they block the transition of tumor cells from G_1 to the S phase of the cell cycle. However, certain endocrine agents (e.g., tamoxifen, progestins) are considered to suppress growth rather than kill tumor cells. Endocrine agents are therefore often given for many years, whereas cytotoxic agents are usually given over a time course measured in months.

An important concept in cancer chemotherapy is that cellular killing with cytotoxic agents follows first-order kinetics, with a given dose of drug killing only a fraction of the tumor cells. This "fractional kill hypothesis" is particularly relevant to CCNS agents and predicts that the greater the dose of drug administered, the greater the "log kill" of tumor cells that will occur.

The concept of combination chemotherapy was developed to take advantage of the fact that many anticancer agents have differing mechanisms of action and side effects. This concept was based on the hypothesis that giving drugs with differing mechanisms of action may achieve synergistic antitumor effects while simultaneously retarding the rate of development of drug resistance. Additionally, by careful selection of drugs in a combination to include those with known single-agent activity against the tumor and different normal tissue toxicities, the side effects would be "spread" across different tissues and organs. The validity of this concept has been borne out clinically. Optimal results for most tumor types sensitive to chemotherapy have been achieved with drug combinations, often employing CCNS and CCS agents possessing different mechanisms of action. For example, cisplatin has demonstrated clear-cut synergy with etoposide in testicular cancer and small cell lung cancer and with fluorouracil in both head and neck and esophageal cancer. The major potential toxicity for cisplatin is nephrotoxicity, whereas myelosuppression is the major side effect for both etoposide and fluorouracil.

New drugs entering clinical trials are normally first tested in patients with a large tumor burden of metastatic cancer who have relapsed from known effective chemotherapy regimens. Although this approach is ethically most acceptable, it nonetheless represents a significant obstacle to new drug development, because these patients have a lower probability of response to a new drug than those with a lower tumor burden or those who have not been previously treated. The presence of the blood-brain barrier has been a major obstacle to the development of chemotherapy for primary or metastatic tumors in the brain. At present, brain tumors are treated chiefly with surgery and radiation therapy.

DRUG RESISTANCE. For many of the drug-responsive tumor types (see Table 198–2), major cytoreduction occurs with initial chemotherapy. Some months to years thereafter, however, tumor regrowth occurs and continues even though the same drugs are reinstituted. This observation usually reflects the acquisition of drug resistance by the tumor to the specific drugs. Most drug resistance is considered to result from the high spontaneous mutation rate of cancer cells, which leads to the development of heterogeneous subpopulations, some of which exhibit resistance to various drugs. Perhaps the most important form of resistance is multidrug resistance (MDR), mediated by a cell membrane glycoprotein (the P-glycoprotein), which is thought to function as an energy-dependent efflux pump that actively extrudes a variety of cytotoxic agents from the cell (Fig. 198–2).

Drugs pumped out of the cancer cell by the P-glycoprotein include natural products such as plant alkaloids (vincas, podophyllotoxins, taxol), antibiotics (dactinomycin, doxorubicin, daunorubicin), and some synthetic agents (e.g., mitoxantrone). The P-glycoprotein is normally expressed in tissues such as the gut and the kidney, perhaps to deal with toxic products in the environment. Cancer cells with mutations to "switch on" the expression of the gene responsible for encoding the P-glycoprotein show resistance to a wide variety of useful anticancer drugs. Techniques such as immunohistochemistry, Western blots, and Northern blots can be used to detect the presence of P-glycoprotein in tumor tissues. Clinical studies suggest that patients whose tumors express P-glycoprotein have a poor prognosis. Culture studies performed on biopsy specimens in vitro have documented that P-glycoprotein–positive tumors usually exhibit resistance to doxorubicin. Tumor types such as sarcoma, neuroblastoma, malignant lymphoma, and myeloma are usually P-glycoprotein negative at the time of diagnosis but are frequently positive for P-glycoprotein when the patient relapses from chemotherapy. A series of non-cytotoxic drugs has been identified to reverse drug resistance mediated by P-glycoprotein (e.g., verapamil, cyclosporine). In drug-resistant patients with malignant lymphoma and multiple myeloma, high doses of verapamil given simultaneously with vincristine and doxorubicin can reverse resistance to these agents, with some patients regaining remission. Although verapamil is not an ideal chemosensitizer (because of its cardiovascular side effects), other potential chemosensitizers are now being tested in an effort to identify more effective and less toxic chemosensitizers. In the long run, such chemosensitizers may find their major use to prevent development of MDR expression. Other mechanisms of multidrug resistance include an increase in proteins called MRP and LRP, and mutations in topoisomerase II, which is the target for the anthracycline drugs and for etoposide.

Drug-specific resistance mechanisms also occur (Table 198–4). For example, intrinsic or natural resistance of patients with acute

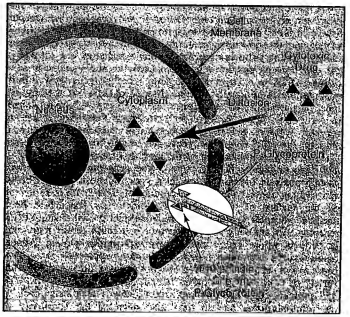

FIGURE 198–2 ■ Model of cancer cell expressing P-glycoprotein. This transmembrane protein is believed to function as an energy-dependent efflux pump or drug transporter. It has acceptor sites to which various natural product anticancer drugs bind, after which they are pumped out of the cell. Chemosensitizers such as verapamil also bind to the drug acceptor sites on P-glycoprotein and can competitively inhibit its function.

Table 198–4 ■ SOME MECHANISMS OF RESISTANCE TO CHEMOTHERAPY DRUGS

DRUG	MECHANISMS OF RESISTANCE
Methotrexate	Impaired transport or amplification of dihydrofolate reductase
Cytarabine	Decreased deoxycytidine kinase or increase in cytidine deaminase
5-Fluorouracil	Increase in thymidylate synthase
Cisplatin	Decreased uptake Increase in repair enzymes
Taxol, *Vinca* alkaloids	MDR expression Mutations in tubulin (decreased binding)
Doxorubicin	MDR expression Decrease or alterations in topoisomerase II
Irinotecan, topotecan	Decrease in topoisomerase I

myelogenous leukemia to methotrexate is attributed to lack of retention of this drug by leukemic blasts. These cells form low levels of methotrexate polyglutamates, the drug species that are retained by cells. In contrast, acute lymphocytic leukemia blasts (pre-B, not T cells) convert methotrexate to its polyglutamates efficiently and are sensitive to treatment with this drug. Acquired resistance, fortunately now noted in the minority of patients with this disease treated with combination chemotherapy, has been found to be associated with impaired uptake due to abnormalities in the reduced folate carrier transport protein, or to low-level amplification of the dihydrofolate reductase gene, whose product is the target for methotrexate.

PREDICTIVE TESTING IN VITRO. Many approaches have been developed to assess the probability of relapse after primary therapy or response to a given type or class of endocrine or cytotoxic agents. The "S-phase" fraction of the tumor cell population undergoing DNA synthesis as well as DNA ploidy can be determined by flow cytometry. For several tumor types, patients with a high percentage of tumor cells in DNA synthesis and/or hyperdiploidy have a high likelihood of relapsing early after local primary cancer therapy. Taken with other prognostic characteristics, such flow cytometry assays may aid in identifying patients who should receive adjuvant chemotherapy. This approach is currently being applied to patients with stage I breast cancer in an effort to decide which patients are at higher risk for recurrence.

Diagnostic laboratories can provide the results of S-phase and DNA ploidy analysis as well as the findings from estrogen and progesterone receptor testing. Estrogen and progesterone receptor assays in breast cancer are used primarily to identify patients likely to respond to endocrine agents in either the adjuvant or recurrent disease setting. The sex steroid hormone receptors are located in the cell nucleus and must bind the hormone and translocate it to cellular DNA to exert endocrine action through gene activation or suppression. Additionally, in the absence of adjuvant therapy, tumors that are estrogen or progesterone receptor positive take longer to recur and have a better overall prognosis than tumors that are receptor negative. Studies have shown that another tumor cell constituent, the *HER-2/neu* oncogene, can be of prognostic value (see Chapter 258). Amplification of the number of copies of the *HER-2/neu* gene or increased expression of the gene product by RNA or protein analysis appears to predict a poor prognosis in both breast and ovarian cancer. The protein product of *HER-2/neu* is expressed on the surface of tumor cells and structurally appears to be a hormone receptor analogous to the epidermal growth factor (EGF) receptor. An antibody to this receptor can cause tumor regression in patients whose breast cancers overexpress this protein. Abnormalities in expression of *p53*, the tumor suppressor gene, have been associated with a worse prognosis when present in a wide variety of solid tumors. Studies indicate that the lack of wild type *p53* protects cells from chemotherapy-induced apoptosis. Lack of the retinoblastoma protein may also decrease the sensitivity of tumor cells to antimetabolites. Thus, measurement of abnormalities of these tumor suppressor genes in tumors may be an additional prognostic factor in treatment outcome.

Chemosensitivity assays appear to predict drug resistance but are somewhat less accurate for predicting which drugs will be useful for an individual patient. Another type of testing for drug resistance that is now being applied to fresh frozen (and in some instances to fixed) tissues is immunohistochemical testing for P-glycoprotein expression.

Knowledge of the mechanism of action of certain drugs has been used to predict sensitivity to these agents. For example, fresh sarcoma cells in short-term mixture have been shown to be useful for evaluating potential anticancer effects of various folate analogues as measured by inhibitors of thymidylate synthesis in a whole-cell assay. In addition, the low levels of thymidylate synthase mRNA expression in tumors has also correlated well with response to fluorouracil treatment among patients with gastric or colon cancer, and studies are in progress to determine if this assay may be used to select patients for treatment with this drug.

PHARMACOKINETIC CONSIDERATIONS. Although intrinsic drug sensitivity appears to be the most critical determinant of response to chemotherapy, pharmacokinetic factors related to the route of administration, bioavailability, metabolism, and elimination are probably of greater importance in cancer therapy. Many cytotoxic agents have a steep dose-response curve and a resulting narrow therapeutic index. Thus, at too low an available dose level within the tumor, no response is seen. On the other hand, at higher doses, host toxicity supervenes and is usually dose limiting. Because of the steep dose-response relationship, doses of most cytotoxic agents are calculated in relation to body surface area, a more accurate approach than dose calculations based on body weight. Patients usually prefer the oral route of drug administration, but marked variations in bioavailability among oral formulations plus inconsistent patient compliance tend to limit such an approach. For example, with the alkylating agent melphalan, more than a 10-fold variation in plasma levels has been documented after standard dosing. Unfortunately, plasma assays are not routinely available for most anticancer drugs, and the only semiquantitative indicator of bioavailability of cytotoxic agents is the occurrence of myelosuppression after drug administration. For patients presenting with hypercalcemia or other complications of myeloma, oral melphalan therefore seems undesirable, because such patients need to achieve effective plasma levels immediately. Similar difficulties are faced with oral administration of fluorouracil; methotrexate, and 6-mercaptopurine. Bioavailability is adequate after oral administration of agents such as tamoxifen and cyclophosphamide.

The intravenous route of drug administration is preferable for most cytotoxic anticancer drugs, because it ensures adequate plasma levels while minimizing compliance problems. For some agents, continuous intravenous drug administration for 4 days or longer provides better results and less toxicity than do bolus or short-duration infusions because tumor response for many agents can be related to the "area under the plasma disappearance curve (AUC)" for the drug, whereas toxicity generally relates more directly to peak plasma concentrations than to the AUC. With the advent of vascular access devices such as subcutaneous ports, external catheters, and infusion pumps, outpatient continuous infusion chemotherapy can now be used for stable drugs such as fluorinated pyrimidines, anthracyclines, and *Vinca* alkaloids. Subcutaneous administration can be used effectively with drugs such as cytarabine, interferon-α, and erythropoietin. Subcutaneous dosing provides more sustained plasma levels than can be obtained with intravenous administration. Depot intramuscular formulations are available for a variety of endocrine agents used in treatment of breast or prostate cancer.

Regional administration of chemotherapy can be effective for several tumor sites. For metastatic colon cancer limited to the liver, hepatic artery catheterization for arterial infusion of 5-fluorodeoxyuridine or 5-fluorouracil can be used effectively by connection of the catheter to an external pump or to an implantable perfusion pump. In either instance, arterial infusions are often administered for 14 days, followed by a similar rest period. A relatively high objective response rate of metastatic colon cancer in the liver can be obtained by this means, but this route is ineffective for metastases outside the liver. Hepatic artery chemotherapy is expensive and associated with complications, including arterial thrombosis, biliary sclerosis, and chemical hepatitis. Nonetheless, it can induce sustained remissions for a year or more in selected patients. Regional infusion or isolated perfusion has been used with melanomas and sarcomas of the lower extremity. With melanoma metastases of the lower extremity, melphalan or cisplatin has been administered in this fashion with or without regional hyperthermia.

Intraperitoneal drug administration has also gained increasing popularity and appears to show particular promise for patients with peritoneal carcinomatosis, where it can induce remissions of established metastatic disease. In ovarian cancer, intraperitoneal chemotherapy is being studied as a follow-up to cytoreductive surgery. Diffusion of intraperitoneally administered drugs is limited to a few millimeters of tumor tissue. Accordingly, intraperitoneal chemotherapy is seldom warranted in patients with bulky tumor masses. For optimal distribution, the drug is usually diluted in 2 L of parenteral fluid for injection. Preferred drugs for intraperitoneal administration are those that tend to be limited largely to the peritoneal cavity, have good properties for tumor penetration, and produce little or no local toxicity. Mitoxantrone, fluorodeoxyuridine, and cisplatin have these favorable characteristics and can be quite useful. With each of these drugs, the intraperitoneal concentration can be 1000-fold higher than measured in the systemic circulation. Other agents sometimes used in intraperitoneal administration include thiotepa, fluorouracil, and methotrexate. Intraperitoneal drug administration can be performed at repeated intervals with relative ease if a surgically implanted Tenkoff catheter is connected to a subcutaneous port. Mild to moderate chemical peritonitis and the development of peritoneal adhesions are common complications of intraperitoneal chemotherapy and limit repeated use. Intracavitary drug administration with instillation of a biologic agent such as bacille Calmette-Guérin (BCG) or interferon or a variety of cytotoxic agents (e.g., thiotepa, doxorubicin, mitomycin, cisplatin) is used to treat superficial bladder cancer.

The intrathecal route can be used to deliver therapy to the meninges. Methotrexate, cytarabine, and thiotepa can be given by this route to prevent meningeal leukemia and treat central nervous system leukemia or lymphoma or meningeal carcinomatosis. Intrathecal methotrexate has been used effectively for acute lymphoblastic leukemia as an adjuvant to initial systemic chemotherapy and has reduced the frequency of central nervous system relapse in patients in complete peripheral remission.

EVALUATION OF RESPONSE. Objective measurement of tumor shrinkage with medical or radiation therapy has prognostic importance. Reduction of symptoms alone does not indicate a response. Cure or significant prolongation of survival occurs in patients who achieve complete response (disappearance of all evidence of cancer). Whenever possible, confirmation of response should be obtained pathologically through the use of restaging procedures. Many patients achieve only a partial response, defined as a reduction of tumor burden by 50% or greater. Patients achieving partial responses generally have palliation of symptoms and usually have a prolonged period without tumor growth. Modest improvements in survival accompany some partial responses.

Tumor markers in the blood or urine can be useful in monitoring response to therapy (see Chapter 192). Patients with testicular germ cell tumors and gestational choriocarcinoma cannot be considered potentially cured unless the titer of marker substance falls below the limit of detection. Tumor marker studies are also useful in judging responses in ovarian cancer, prostatic carcinoma, colon cancer, multiple myeloma, neuroblastoma, and the carcinoid syndrome.

Response to adjuvant chemotherapy cannot be evaluated by these methods, because insufficient tumor usually remains to employ physical or imaging studies or tumor markers. However, in the neoadjuvant setting in which chemotherapy is used before local surgery, the response to chemotherapy provides an "in vivo sensitivity test" to determine whether the employed agents can provide effective therapy after surgery.

CYTOTOXIC ANTICANCER DRUGS. Safe and effective cytotoxic cancer chemotherapy requires considerable understanding of the pharmacology and toxicology of these drugs. Drug doses are cited for single-agent chemotherapy; when drugs are used in combinations (Table 198–5), lower doses may be required for some agents. Therefore, it is wise to use effective and well-established combination protocols with known side-effect profiles rather than to improvise combinations. The development of new combinations of standard drugs is best done in the research setting.

ALKYLATING AGENTS. The major clinically useful alkylating agents (Table 198–6) kill cells by binding to and cross-linking DNA through a bis(chloroethyl)amine, ethyleneimine, or nitrosourea moiety. Although these agents likely kill cells by alkylating DNA (primarily at the N7 position of guanine), they also react chemically with nucleophilic molecules (e.g., sulfhydryl, amino, hydroxyl, and phosphate groups). Alkylating agents differ in the severity of early and late side effects. The major acute side effects are gastrointestinal (nausea and vomiting) and hematologic (myelosuppression). Most alkylating agents cause local skin and subcutaneous tissue necrosis when infiltrated into the skin.

All alkylating agents can potentially induce ovarian or testicular failure as well as acute leukemia. Agents such as melphalan and chlorambucil appear to be more leukemogenic than cyclophosphamide, whereas busulfan and the nitrosoureas cause more persistent damage to hematopoietic stem cells and more prolonged myelosuppression.

Cyclophosphamide and Ifosfamide. Cyclophosphamide (Cytoxan) is the most widely used alkylating agent and is effective in the treatment of both hematologic malignancies and solid tumors. It does not have significant vesicant effects, because it is a prodrug that requires bioactivation in the liver. Metabolism of cyclophosphamide by cytochrome P-450 produces the active metabolite phosphoramide mustard plus acrolein. Cyclophosphamide is available in both intravenous and oral formulations and is well absorbed by the oral route. A commonly used single-agent dosage schedule for intravenous cyclophosphamide is 1.0 g/m^2 every 3 weeks. Cyclophosphamide produces a less severe pattern of myelosuppressive toxicity than other alkylating agents; it can cause severe neutropenia but usually of relatively short duration, and thrombocytopenia is less severe than with other alkylators. Other toxicities of cyclophosphamide include alopecia and immunosuppression. When high doses are used (e.g., for bone marrow transplantation), cyclophosphamide can also cause myocardial necrosis or the syndrome of inappropriate secretion of antidiuretic hormone. Although cyclophosphamide can cause acute non-lymphocytic leukemia and pulmonary fibrosis, these toxicities are more common with other alkylating agents. Both cyclophosphamide and a related analogue, ifosfamide (Ifex), can cause hemorrhagic cystitis. Bladder toxicity can be blocked by administration of the uroprotective agent mesna (Mesnex), which is concentrated in the urine and inactivates the toxic metabolite acrolein. Mesna is particularly valuable with ifosfamide, which otherwise routinely causes bladder toxicity. Ifosfamide causes somewhat less hematologic toxicity than other alkylating agents and at present is used mostly for second-line therapy (e.g.,

Table 198–5 ■ COMMON COMBINATION CHEMOTHERAPY REGIMENS

ABBREVIATION	DRUGS EMPLOYED	INDICATION
MOPP	Nitrogen mustard (Mustargen), vincristine (Oncovin), prednisone, procarbazine	Hodgkin's disease
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine	Hodgkin's disease
CHOP	Cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), prednisone	Non-Hodgkin's lymphomas
CMF	Cyclophosphamide, methotrexate, 5-fluorouracil	Breast cancer
CAF	Cyclophosphamide, doxorubicin (Adriamycin), 5-fluorouracil	Breast cancer
M-VAC	Methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin	Bladder cancer
PVB	cisplatin, vinblastine, bleomycin	Testicular cancer
VAD	Vincristine, doxorubicin (Adriamycin), dexamethasone	Multiple myeloma

Table 198–6 ■ ALKYLATING ANTICANCER DRUGS

RUG	MAJOR INDICATIONS
litrogen mustard	Hodgkin's disease
delphalan	Multiple myeloma
hlorambucil	Chronic lymphocytic leukemia
usulfan	Chronic myelocytic leukemia
yclophosphamide	Lymphoma, breast cancer, bladder cancer
osfamide	Soft tissue sarcoma, lymphoma
litrosoureas (carmustine, lomustine)	Brain tumors, lymphoma
rocarbazine	Hodgkin's disease
lacarbazine	Melanoma, Hodgkin's disease
isplatin, carboplatin	Testicular, ovarian cancer, head and neck, lung cancer

or therapy for testicular cancer, lymphoma, or metastatic sarcomas).

Chlorambucil. Chlorambucil (Leukeran) has antitumor activity similar to that of cyclophosphamide and is also well absorbed after oral administration. It is used primarily in the treatment of chronic lymphocytic leukemia, low-grade lymphomas, macroglobulinemia, and polycythemia vera. Chlorambucil does not cause hemorrhagic cystitis or alopecia, and its gastrointestinal side effects are mild. However, it is myelosuppressive. Acute non-lymphocytic leukemia has been reported in patients treated with chlorambucil for polycythemia vera or other disorders.

Melphalan. Melphalan (Alkeran) is L-phenylalanine mustard and gains access to cells through an amino acid transport system. Melphalan is commonly given orally in a dosage of 10 mg/m^2/day for days every 3 to 4 weeks. Some patients do not absorb the drug; rather, the only clue, other than drug levels, is the absence of myelosuppression. If myelosuppression does not occur, melphalan dosage should be increased in subsequent courses until moderate myelosuppression is induced. Melphalan is commonly used in the treatment of multiple myeloma and ovarian cancer and occasionally for other tumor types. The drug induces acute non-lymphocytic leukemia in some patients treated for myeloma or ovarian cancer.

Busulfan. Busulfan (Myleran) is a methane-sulfonate–based alkylating agent that has specificity for myeloid neoplasms and appears to have less antitumor activity in other forms of cancer. It is available only for oral administration and is used primarily for treatment of chronic myeloid leukemia (CML) or as part of marrow ablative regimens followed by stem cell transplantation. Busulfan can produce protracted myelosuppression, and hematologic recovery should be complete before the next course is administered. Busulfan can also cause pulmonary fibrosis, hyperpigmentation, cachexia, and wasting. Adrenal function remains normal.

Nitrosoureas. Carmustine (BCNU) and lomustine (CCNU) are rapidly biotransformed through non-enzymatic hydrolysis to release intermediates with alkylating and carbamoylating activities. Carmustine is available for intravenous use, and lomustine is given orally. The major toxicity of nitrosoureas at standard dosage levels is on hematopoietic stem cells; delayed, prolonged myelosuppression can result. At high doses (e.g., in preparative regimens for bone marrow transplantation), nitrosoureas can induce a chemical hepatitis or pneumonitis. Prolonged use with total doses greater than 1500 mg/m^2 can also result in pulmonary fibrosis or renal failure. Because of their high lipid solubility and ability to cross the blood-brain barrier, the nitrosoureas have some activity against primary brain tumors. The nitrosoureas also are useful in the management of Hodgkin's disease and multiple myeloma and as part of combined-modality therapy for cancers of the anal canal.

Platinum Compounds. Cisplatin and carboplatin are platinum-coordination compounds with broad-spectrum antitumor activity and synergistic interactions with a variety of other cytotoxic agents, including alkylating agents, antimetabolites, and natural products. Although their mechanism of action is not completely understood, they act similarly to alkylating agents in terms of their ability to bind to the N7 position of guanine and crosslink DNA. However, cross-linking with adenine and cytosine also occurs, as does binding to RNA and protein.

Cisplatin and carboplatin differ in their toxicity profiles. Both drugs are administered intravenously. Cisplatin is commonly given in a dose of 100 mg/m^2 every 3 weeks, whereas the dose of carboplatin is in the range of 450 mg/m^2 at similar intervals, although larger doses may be tolerated. After intravenous infusion, the major acute toxicity for both cisplatin and carboplatin is nausea and vomiting, which is worse with cisplatin. Satisfactory suppression of the gastrointestinal side effects of platinum compounds requires potent antiemetic agents, often in combination. Large cumulative doses of cisplatin also cause renal toxicity, which can be largely prevented if the patient is well hydrated with simultaneous saline infusions and diuretics. Large cumulative doses can also cause a progressive neuropathy. Myelosuppression is minimal with cisplatin but is dose limiting with carboplatin. Although carboplatin is less toxic than cisplatin, its efficacy is equivalent for some, but not all, tumors. The lack of myelosuppression favors cisplatin for use in some drug combinations with myelosuppressive agents. A new platinum analogue, oxaloplatin, may have activity against colon cancer comparable with that of fluorouracil.

ANTIMETABOLITES. The antimetabolites (Table 198–7) are structural analogues of normal biochemical compounds, most of which are involved in DNA or RNA synthesis and generally function as CCS agents. Antimetabolites are classed in relation to their mechanisms of action.

Pyrimidine Antagonists. *Cytarabine (Cytosine Arabinoside, Cytosar-U, Ara-C).* Cytarabine is an S-phase–specific agent that is particularly useful in acute non-lymphocytic leukemia and, to a lesser extent, in other hematologic malignancies. Its active form, ara-CTP, competitively inhibits DNA polymerase, blocking DNA synthesis. Ara-C also blocks chain elongation and ligation of fragments into newly synthesized DNA. Ara-C is given intravenously and crosses the blood-brain barrier. It is administered either by continuous infusion or in bolus doses by the intravenous or subcutaneous route for 5 to 7 days. In an alternative schedule that exceeds the manufacturer's recommended maximum, high-dose ara-C is administered in doses of 1 to 3 g every 12 hours for 3 to 5 days and yields higher response rates. The duration of intracellular retention of ara-CTP appears to predict ara-C antileukemic effects, with best results in patients who have the longest ara-CTP retention times. Both standard and high-dose ara-C can produce severe myelosuppression. With the high-dose regimen, chemical conjunctivitis is common and can be ameliorated with corticosteroid ophthalmic drops. With rare exception, complete remissions can be achieved in acute leukemia only if ara-C is administered with sufficient intensity to drive the bone marrow to severe hypocellularity and destroy the leukemic blast population. Thereafter, the marrow is repopulated by residual normal progenitors that were suppressed by the leukemia. Ara-C is generally used in combination with daunorubicin in the treatment of acute non-lymphocytic leukemia but also acts synergistically with other drugs, including cisplatin. Cytarabine can also be given intrathecally in doses of 75 to 100 mg as treatment for leukemic or carcinomatous meningitis.

Gemcitabine. Gemcitabine (Gemzar), is a novel nucleoside analogue with structural similarities to cytarabine. Both drugs are metabolized by cytidine deaminase and require intracellular phos-

Table 198–7 ■ ANTIMETABOLITE ANTICANCER DRUGS

DRUG	MAJOR INDICATIONS
Folic acid antagonists (methotrexate)	Acute lymphocytic leukemia, choriocarcinoma, breast cancer, bladder cancer, head and neck cancer, lymphoma
5-fluorouracil	Gastrointestinal cancer, breast cancer, cancer of the head and neck
5-fluorodeoxyuridine	Regional therapy (intra-arterial or intraperitoneal) for colon cancer metastasis
Cytarabine	Acute leukemia
Gemcitabine	Cancer of the pancreas
6-Mercaptopurine, 6-thioguanine	Acute leukemia
Fludarabine	Chronic lymphocytic leukemia, low-grade lymphoma
2-Chlorodeoxyadenosine	Hairy cell leukemia, low-grade lymphoma
Deoxycoformycin	Hairy cell leukemia, T-cell lymphoma
Hydroxyurea	Chronic myelocytic leukemia

phorylation for activation. The drug is approved for use in the treatment of patients with advanced pancreatic carcinoma. Gemcitabine significantly improves disease related symptoms in approximately 25% of patients, and a modest increase in survival was demonstrated in patients with pancreatic carcinoma when compared with treatment with 5-fluorouracil. The drug is well tolerated; reversible myelosuppression is the dose-limiting toxicity. The drug is administered intravenously over 30 minutes, weekly for 3 weeks followed by 1 week of rest.

Fluorouracil and Floxuridine. Fluorouracil (5-FU) is an important anticancer agent used to treat a variety of solid tumors, including cancers of the head and neck, esophagus, breast, and colon. It acts synergistically with a variety of agents, including platinum compounds and radiation therapy. Studies indicate that "pulse" or bolus injections of 5-FU are cytotoxic mainly as a result of incorporation into RNA, whereas continuous infusions of this drug (2 or more days) kill cells by inhibiting DNA synthesis and producing "thymine-less death." 5-FU is usually given intravenously by bolus or infusion schedules but can also be used in intra-arterial, intracavitary, and topical therapy. An optimal schedule for 5-FU administration is a 5-day continuous infusion at a dose rate of 1.0 g/m²/day. This schedule causes some gastrointestinal toxicity but only a mild degree of myelosuppression. Full doses of cisplatin can be administered additionally, providing an active treatment program in the neoadjuvant chemotherapy of head and neck and esophageal cancer. 5-FU administered on a weekly intravenous bolus schedule produces greater hematologic toxicity and mucositis than lower total doses. Less common toxicities observed with 5-FU include a neurologic syndrome associated with ataxia, chemical conjunctivitis, and a syndrome including chest pain and cardiac enzyme elevation consistent with myocardial ischemia. The bioavailability of 5-FU after oral administration is erratic, and the drug is metabolized mostly during its first pass through the liver.

Both the gastrointestinal toxicity and the antitumor activity of 5-FU can be enhanced by administration of leucovorin, which increases the binding of fluorodeoxyuridine phosphate to thymidylate synthase. This combination appears to increase the antitumor activity of 5-FU in breast and colon cancer. Interferon-α and levamisole also appear to enhance 5-FU activity in colorectal cancer. Levamisole potentiation has been observed only in the adjuvant setting. Recent studies showed that 6 months of treatment with 5-FU and leucovorin in the adjuvant setting is the regimen of choice for patients with colorectal cancer. Both 5-FU and floxuridine (5-FUDR) can be given by hepatic artery infusion to treat patients with colorectal carcinoma with metastases confined to the liver. With the use of a surgically placed vascular access catheter, outpatient hepatic artery infusions can be administered using either an internal or a portable external pump. A limitation is that either 5-FU or 5-FUDR can induce a chemical hepatitis and biliary sclerosis with jaundice. Hepatic dysfunction can be most readily detected by obtaining liver chemistries on day 14 when 5-FU is to be discontinued. Studies indicate that the response rate and duration of remission are increased by the addition of leucovorin (folinic acid) or dexamethasone to 5-FUDR.

Purine Antagonists. *6-Mercaptopurine and 6-Thioguanine.* In contrast to 6-mercaptopurine (6-MP), some 6-thioguanine (6-TG) metabolites are incorporated into both DNA and RNA. 6-TG has some uses in acute non-lymphocytic leukemia in combination with cytarabine, whereas 6-MP is used primarily in acute lymphoblastic leukemia, particularly in childhood. Absorption of 6-MP is variable, but plasma monitoring can identify poor absorbers who have a high likelihood of developing recurrent leukemia, presumably because of inadequate bioavailability of 6-MP. The 6-MP analogue azathioprine is a useful immunosuppressive agent. Because both 6-MP and azathioprine are catabolized by xanthine oxidase, patients must have their thiopurine doses reduced to 25% of their standard doses if they are also receiving the xanthine oxidase inhibitor allopurinol. 6-TG is not catabolized by xanthine oxidase, and dose correction is not required for allopurinol.

Fludarabine. Fludarabine (Fludara, 5-fluoroadenosine monophosphate) is an analogue of adenine that inhibits DNA polymerase and ribonucleotide reductase. Fludarabine is the single most active agent available in the treatment of chronic lymphocytic leukemia and also exhibits some antitumor activity in other indolent lymphomas and macroglobulinemia. Fludarabine is often given intravenously in a dose of 25 mg/m²/day over 30 minutes for 5 days every 4 weeks. The major toxicity is myelosuppression. Higher doses administered in early trials in patients with acute non-lymphocytic leukemia occasionally produced cortical blindness. In the lower-dosage schedule used in chronic lymphocytic leukemia and other lymphoid neoplasms, side effects are usually mild and reversible.

Additional purine antagonists include deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CDA). Both DCF and 2-CDA are extremely active agents in the treatment of hairy cell leukemia and can produce prolonged remissions after a single course of treatment. Both agents also exhibit some antitumor activity in other low-grade lymphoid neoplasms (e.g., CLL and low-grade lymphomas).

Folic Acid Antagonists. Methotrexate (MTX) is a structural analogue of folic acid and is currently the only FDA-approved member of this group. Clinical trials of new antifolates are targeting not only dihydrofolate reductase (e.g., trimetrexate) but also other folate-requiring enzymes such as thymidylate synthase (e.g., raltitrexed). MTX can be administered orally, intramuscularly, or intravenously and is useful primarily as a component of chemotherapy combinations for various types of cancer, including acute lymphoblastic leukemia, small cell lung cancer, bladder cancer, head and neck cancer, and breast cancer. When used in high dosage with leucovorin rescue, it exerts antitumor activity in osteogenic sarcoma. Intracellular formation of polyglutamated forms of MTX is important to the action of MTX, because the polyglutamated forms have equivalent ability to inhibit dihydrofolate reductase action but have a longer intracellular retention time than MTX. The polyglutamates also inhibit other folate-dependent enzymes, including thymidylate synthase. Given satisfactory renal function and adequate hydration, MTX is excreted unchanged mainly in the urine within 12 hours of administration.

Major toxicities of MTX are to rapidly dividing tissues, including the bone marrow, gastrointestinal mucosa, and, to a lesser extent, skin. At high dosages or in patients with impaired renal function, MTX also can induce renal toxicity. Chronic extended use of MTX (e.g., for maintenance treatment of patients with acute lymphocytic leukemia or long-term treatment of patients with psoriasis), occasionally leads to liver fibrosis and cirrhosis. The toxic effects on the rapidly dividing tissues can be circumvented by administering the reduced folate leucovorin (folinic acid) within 36 hours after MTX administration. Leucovorin rescue also can be used when MTX is intentionally administered in higher than manufacturer's recommended maximum dose (e.g., 1500 mg/m² or more). When high-dose MTX is administered, leucovorin must be administered 24 to 36 hours after MTX in dosages of 15 to 50 mg/m² every 6 hours for 48 hours, with the duration of rescue contingent on the serum MTX level. Increased leucovorin dosage and longer periods of rescue are needed in patients with impaired renal function. The high-dose MTX/leucovorin rescue regimen therefore requires good renal function.

NATURAL PRODUCT ANTICANCER DRUGS. The two main classes of natural antitumor products are plant alkaloids and antibiotics (Table 198–8). Resistance to the natural products, with the exception of bleomycin, can be mediated by the P-glycoprotein multidrug resistance mechanism.

PLANT ALKALOIDS. Vincristine and Vinblastine. The *Vinca* alkaloids were isolated from the common periwinkle (*Vinca roxaeca*). The major Vinca alkaloids in clinical use, vincristine (Oncovin) and vinblastine (Velban), precipitate tubulin and disrupt cellular microtubules. Whereas the primary toxicity of vinblastine is hematopoietic, vincristine's major toxicity affects peripheral nerves, resulting in sensorimotor and autonomic neuropathies. Common symptoms are paresthesias ("pins and needles sensation") in the digits and progressive muscular weakness with areflexia, particularly in the lower extremities. Footdrop can develop, as can occasional cranial, bladder, or bowel neuropathies. The neurotoxicity subsides slowly after the drug is discontinued, with improvement requiring months, especially if motor function is impaired. The lack of bone marrow toxicity of vincristine has made it useful for combination chemotherapy regimens. The *Vinca* alkaloids have vesicant effects and can be administered only intravenously. Both provide antitumor activity in leukemias and lymphomas as well as in selected solid tumors, including small cell lung cancer and breast cancer. Vincristine is used in various drug combinations, in-

Table 198-8 ■ NATURAL PRODUCT ANTICANCER DRUGS

DRUGS	MAJOR INDICATIONS
Plant Alkaloids	
Vincristine	Lymphoid malignancies
Vinblastine	Hodgkin's disease, testicular cancer
Vinorelbine	Small cell lung cancer
Podophyllotoxins	
Etoposide (VP-16)	Small cell lung cancer, lymphoma
Teniposide (VM-26)	Acute lymphocytic leukemia
Paclitaxel (Taxol)	Ovarian cancer, breast cancer
CPT-11	Colon cancer
Antibiotics	
Anthracyclines	
Doxorubicin	Lymphoma, breast cancer, sarcomas
Daunorubicin	Acute leukemia
Idarubicin	Acute leukemia
Mitoxantrone (synthetic)	Acute leukemia, lymphoma
Mitomycin	Gastrointestinal malignancies
Dactinomycin	Choriocarcinoma, Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma
Bleomycin	Lymphoma, head and neck cancer
Miscellaneous Agents	
Hexamethylmelamine	Ovarian cancer
Asparaginase	Acute lymphocytic leukemia

cluding MOPP, CHOP, MACOP-B, and M-BACOD for the treatment of lymphomas (see Chapter 179), and VMCP and VAD in the treatment of multiple myeloma (see Chapter 181). Vinblastine's greatest use has been in its incorporation into the PVB regimen for the treatment of non-seminomatous testicular cancers (see Chapter 247), and in the ABVD regimen to treat Hodgkin's disease (see Chapter 180). Vinblastine is also used in combination with cisplatin in non–small cell lung cancer and with mitomycin in metastatic breast cancer.

Vinorelbine. Vinorelbine (Navelbine) is a semisynthetic *Vinca* alkaloid approved for use in the treatment of non–small cell lung cancer. Its spectrum of antitumor activity and its mechanism of action are similar to those of vinblastine and vincristine. In humans, its limiting toxicity, like that of vinblastine is hematologic, and its spectrum of activity and use in combinations is under investigation.

PODOPHYLLOTOXINS. Etoposide. Etoposide (VP-16, VePesid), a semisynthetic glucoside, is produced from extracts of the root of the mayapple or mandrake (*Podophyllum peltatum*). A closely related analogue, teniposide (VM-26), has not been approved in the United States by the FDA. Mechanistically, podophyllotoxins are thought to act as inhibitors of nuclear topoisomerase II, leading to DNA strand breaks. Additional effects include inhibition of nucleoside transport and mitochondrial electron transport. Etoposide is highly lipid soluble and water insoluble and requires a special formulation for intravenous administration. An oral formulation is also available. Good tissue distribution is achieved in all sites other than the brain. A commonly used schedule administers etoposide intravenously for 3 days at a dosage of 150 to 200 mg/m^2/day. Etoposide is excreted primarily in the urine and to a lesser extent in the bile. Its dosage should be reduced by half in patients with impaired renal function. The main side effect is myelosuppression, although gastrointestinal toxicity and alopecia also can occur. Etoposide is used primarily to treat metastatic testicular cancer in combination with cisplatin and bleomycin. The combination substitutes etoposide for vinblastine, yielding a less toxic but equally effective regimen. Etoposide also exerts potent effects against small cell lung cancer, lymphomas, and monocytic leukemia.

Paclitaxel. The taxoids are an important new class of anticancer agents that appear to stabilize tubulin as their major mechanism of action. Paclitaxel (Taxol) has been approved for use in the United States for the treatment of breast cancer and ovarian cancer and is also widely used for other epithelial tumors (head and neck, esophagus, non–small cell lung cancer) in combination therapy regimens. For example, the combination of cisplatin and paclitaxel is now first line treatment with a 10 to 20% cure rate for patients with ovarian cancer, where it improves survival compared with cisplatin and cyclophosphamide. The drug may cause hypersensitivity reactions (e.g., hypotension, dyspnea, bronchospasm and urticaria). Typically, premedications are administered before paclitaxel administration to prevent these reactions: dexamethasone, 20 mg orally or intravenously, 12 and 6 hours before treatment; diphenhydramine, 50 mg, 30 minutes before treatment; and an H_2 antagonist (e.g., cimetidine), 300 mg, intravenously, 30 minutes before treatment. Other toxicities include neutropenia, which is dose limiting, myalgias, and peripheral neuropathy, the latter which generally occurs only after multiple courses at conventional doses (135 to 250 mg/m^2 over 24 hours). Other dosage schedules (3-hour, 96-hour) are under investigation.

Docetaxel. Docetaxel (Taxotere) is a semisynthetic analogue of paclitaxel and has been approved for use in the treatment of locally advanced or metastatic breast cancer that has progressed during anthracycline-based therapy. This drug also has anticancer activity in patients with non–small cell lung cancer. The recommended dose is 60 to 100 mg/m^2 intravenously every 3 weeks.

ANTITUMOR ANTIBIOTICS. Doxorubicin, Daunorubicin, and Idarubicin. These anthracycline antibiotics were isolated from a variant of *Streptomyces peucetius* and are extremely useful in cancer chemotherapy. Daunorubicin (daunomycin) was the first agent in this class and is active in the treatment of acute leukemia. Its congener, doxorubicin (Adriamycin), has a broader spectrum of antitumor activity, including both hematologic malignancies and a variety of solid tumors such as carcinoma of the breast and thyroid, lymphoma, and myeloma, as well as osteogenic and soft tissue sarcomas. Daunorubicin is frequently used in combination with cytarabine in the treatment of acute myelocytic leukemia, whereas doxorubicin is incorporated into regimens for solid tumors along with cyclophosphamide, fluorouracil, etoposide, vincristine, or cisplatin. Mechanistically, the anthracyclines intercalate with high affinity into DNA and inhibit the action of topoisomerase II, resulting in DNA strand breaks. Anthracycline cardiac toxicity may also be related in part to the generation of free radicals. Both doxorubicin and daunorubicin must be administered intravenously by either bolus injection or prolonged infusion. Extravasation can lead to severe tissue injury. Immediate topical application of 1.5 mL of 99% dimethylsulfoxide (DMSO) has been reported to prevent subsequent ulceration. For prolonged anthracycline infusions, use of a vascular access catheter is advisable. Ulceration and necrosis after anthracycline extravasation usually require surgical débridement of the damaged tissues plus skin grafting.

The most common acute toxicities of the anthracyclines include alopecia, nausea, vomiting, mucositis, and myelosuppression. A dose-dependent, delayed, and potentially irreversible cardiomyopathy with reduced cardiac contractility can develop in patients who receive large cumulative doses of doxorubicin or daunorubicin (see Chapter 64). Acute cardiac arrhythmias are uncommon.

Periodic monitoring for cardiac effects of anthracyclines is normally initiated when a patient has received a total doxorubicin dose of 350 to 400 mg/m^2. Endomyocardial biopsy can also be used. Cardiac toxicity is uncommon with cumulative bolus doses of doxorubicin of less than 550 mg/m^2, above which the incidence rises progressively. Elderly patients and others with risk factors for cardiac disease (e.g., hypertension) are at somewhat higher risk for anthracycline cardiomyopathy. Anthracyclines are not recommended for patients who have major pre-existing heart disease. When doxorubicin is administered by continuous infusion (e.g., for 4 to 5 days), there is less cardiotoxicity, and a significantly larger cumulative dose in the range of 1000 mg/m^2 can usually be administered. However, regular cardiac monitoring is required, and doxorubicin should be discontinued if the left ventricular ejection fraction falls by 15 percentage points and to below 50%. Idarubicin is another anthracycline recently approved for use in the treatment of acute myelocytic leukemia. In controlled studies, idarubicin in combination with cytarabine induced higher remission rates than daunorubicin and cytarabine.

An agent that protects the heart from anthracycline toxicity, dexrazoxane, has been approved for use by the FDA for patients who are treated with cumulative doses of doxorubicin greater than 300 mg/m^2. Liposomal preparations of doxorubicin are also being evaluated as potentially less cardiotoxic formulations. Toxicities associated with dexrazoxane are pain at the injection site and modest neutropenia and thrombocytopenia. The possibility that dexrazoxane may have an adverse effect on tumor response led to the FDA rec-

ommendation that treatment with this drug should be initiated only when the cumulative dose of 300 mg/m² of doxorubicin was reached.

Bleomycin. Bleomycin (Blenoxane) comprises 11 closely related glycopeptide moieties produced by *Streptomyces verticillus*. The major components are bleomycins A2 and B2. Bleomycin action involves its binding to DNA and generation of superoxide and other reactive oxygen species, including hydroxyl radicals. DNA fragmentation appears to result from the oxidation of a DNA-bleomycin-Fe^{2+} complex. Bleomycin's antitumor activity is schedule dependent, acting primarily at the G_2 phase of the cell cycle. It can be administered by subcutaneous, intramuscular, and intravenous routes. Its major uses are in combination therapy to treat carcinoma of the testis and squamous cell carcinomas of the head and neck, cervix, skin, penis, and rectum. It is also used in combination regimens for treatment of lymphomas (ABVD).

Bleomycin has minimal myelosuppressive effects and is useful in combination with drugs that cause leukopenia. Acute toxicities include anaphylactoid reactions and fever associated with hypotension and dehydration. Patients who have not received bleomycin previously should receive a test dose (e.g., 1 to 2 mg) to discover such adverse reactions. Individual therapeutic doses of bleomycin are usually in the range of 5 to 10 units/m².

The most serious chronic reaction to bleomycin is pulmonary fibrosis related to the cumulative dose of drug and manifested by cough, dyspnea, and bilateral basilar infiltrates on chest radiography. It is possible to screen for earlier pulmonary abnormalities such as a decline in the diffusion capacity, which is usually detectable at total doses of bleomycin above 250 units. If the pulmonary diffusion capacity falls abnormally, bleomycin should be discontinued. The incidence of pulmonary fibrosis rises at total doses above 450 units and is higher in patients with pre-existing pulmonary disease, after lung irradiation, and in the elderly. This toxicity may be irreversible, although corticosteroids may be of some use. Other reactions to bleomycin include skin toxicity with blistering, desquamation, hyperkeratosis of the palms, and hyperpigmentation of creases.

Mitomycin. Mitomycin (Mutamycin, Mitocin-C, Mitomycin C) is isolated from *Streptomyces caespitosus*. Its structure includes quinone, carbamate, and aziridine groups, which may contribute to its antitumor activity. Mitomycin functions as a CCNS alkylating agent after it has been activated in various tissues by the cytochrome P-450 system. Thereafter, it can alkylate DNA to form intrastrand and interstrand crosslinks resulting in cell death. Mitomycin has "bioreductive" properties, with increased cytotoxic effects on poorly oxygenated tumor cells in solid tumors, and has been used in combination with irradiation to treat patients with cancer of the head and neck. Mitomycin's clinical spectrum of antitumor activity includes breast, lung, gastrointestinal, genitourinary, and gynecologic cancers. Mitomycin has been incorporated into a variety of cytotoxic drug combinations for systemic administration, often as second-line therapy for patients who relapse from initial chemotherapy. It is usually administered intravenously but can be used for intravesical therapy of superficial bladder cancer. Its normal intravenous dosage range is 10 to 15 mg/m².

The major toxicity of mitomycin is delayed myelosuppression, usually appearing 4 to 6 weeks after injection. Mitomycin has a cumulative effect on bone marrow stem cells, which can lead to protracted marrow hypoplasia for 3 to 6 months after discontinuing the drug. Nausea, vomiting, and anorexia often occur at the time of administration but can usually be managed effectively with antiemetic agents. Occasionally, mitomycin can induce interstitial pneumonitis, nephrotoxicity, or hemolytic-uremic syndrome.

Dactinomycin. Dactinomycin (Actinomycin D, Cosmegen) was the first effective antitumor antibiotic isolated from *Streptomyces*. It binds to the DNA helix by intercalation between adjacent guanine-cytosine base pairs; it inhibits DNA-dependent RNA synthesis and leads to cessation of most protein synthesis in sensitive cells. The drug is administered intravenously, and its major toxicity is myelosuppression, usually appearing 7 to 10 days after injection. Dactinomycin also causes significant gastrointestinal toxicity with abdominal cramps and diarrhea as well as mucositis. The drug also can cause a radiation "recall" reaction in which cutaneous erythema redevelops at a site of prior irradiation. The principal use of dactinomycin is in pediatric oncology in combination chemotherapy for the treatment of Wilms' tumor, Ewing's sarcoma, and embryonal rhabdomyosarcoma. It has some utility in adults in third-line therapy of germ cell tumors of the testis or ovary, gestational choriocarcinoma, and soft tissue sarcomas.

TOPOISOMERASE I INHIBITORS. This class of drugs binds to topoisomerase I. Two inhibitors of this enzyme have now been approved for clinical use: irinotecan and topotecan.

Irinotecan. Irinotecan (CPT-11, Camptosar) is a prodrug that is rapidly hydrolyzed in vivo to SN-38, a potent inhibitor of topoisomerase I. It has been approved for use in the treatment of patients with colorectal cancer. The dose schedule used most commonly is a single infusion (200 mg/m²) every 3 weeks, although other dose schedules are being explored. The principal dose-limiting toxicities are non-hematologic, in particular diarrhea. Diarrhea may be seen within the first 24 hours of treatment, or later, occurring 4 to 8 days after treatment. Aggressive treatment with loperamide or octreotide at the first sign of diarrhea has allowed patients to tolerate this drug. Severe neutropenia may also occur with CPT-11. Current studies are evaluating combinations of this drug with fluorouracil or raltitrexed (Tomudex), an investigational drug that targets the enzyme thymidylate synthase.

Topotecan. Topotecan (Hycamtin) is approved for use in previously treated patients with ovarian cancer. Its mechanism of action is similar to that of irinotecan, namely, inhibition of topoisomerase I. Topotecan also has activity in other tumors, including hematologic malignancies, small cell lung cancer, neuroblastoma, and rhabdomyosarcoma. The recommended dose is 1.5 mg/m²/day infused intravenously over 30 minutes for 5 consecutive days, every 3 weeks. The dose limiting and most common toxicity is myelosuppression, especially neutropenia.

MISCELLANEOUS ANTICANCER AGENTS. PROCARBAZINE. Procarbazine (Matulane) is an orally administered methylhydrazine derivative that has antitumor activity in Hodgkin's disease (as part of MOPP combination chemotherapy) and in non-Hodgkin's lymphomas, lung cancer, and brain tumors. Procarbazine is usually given in a dose of 100 mg/m²/day for 10 to 14 days in each chemotherapy cycle. Procarbazine is activated metabolically to produce a methyldiazonium ion that binds to nucleic acids, proteins, and phospholipids to inhibit macromolecular synthesis. Its mechanism of cytotoxicity is thought to involve DNA strand scission, possibly through generation of H_2O_2. Procarbazine's principal toxicities are nausea, vomiting, and myelosuppression. One of procarbazine's metabolites is a monoamine oxidase (MAO) inhibitor that can cause toxicity when the patient is taking other MAO inhibitors. Patients taking procarbazine may develop hypertension if they ingest tyramine-rich foods such as ripe cheese, wine, and bananas. Disulfiram-like reactions are also seen, with sweating and headache after alcohol ingestion. Other infrequent reactions include hemolytic anemia and pulmonary reactions. Procarbazine is also known to be leukemogenic, carcinogenic, and mutagenic and is considered to play a significant role in the development of late leukemias and other second malignancies in patients with Hodgkin's disease. Procarbazine also produces azoospermia and anovulation. Because alternative combinations lacking procarbazine can be used in the treatment of Hodgkin's disease (e.g., ABVD), the benefits versus risks of using this agent must be carefully considered.

DACARBAZINE. Dacarbazine (DTIC, dimethylimidazole carboxamide) is activated by oxidative *N*-demethylation. A methyl carbonium ion metabolite is thought to be the cytotoxic intermediate with alkylating activity. Dacarbazine is administered intravenously either in a single-day infusion schedule of 750 mg/m² or in fractionated bolus doses over 5 days or more. DTIC causes severe nausea and vomiting, and potent antiemetic agents are required. Myelosuppression is relatively mild. Dacarbazine is used in combination chemotherapy for Hodgkin's disease (ABVD), for soft tissue sarcomas in combination with doxorubicin and other agents, and in single-agent chemotherapy for metastatic melanoma.

HEXAMETHYLMELAMINE (HMM). This agent is available only in an oral formulation because of its sparing solubility. Oral bioavailability of HMM is quite variable, however, and nausea and vomiting can be dose limiting. The gastrointestinal distress increases with daily use, limiting the length of treatment courses (at doses of up to 12 mg/kg/day) to 2 to 3 weeks. Mild myelosuppression occurs. Additionally, HMM can induce both central and peripheral neurotoxicities, including altered mood, hallucinations, and peripheral

neuropathy. HMM is thought to act as an alkylating agent, possibly through the enzymatic hydroxylation of its demethyl metabolites to cytotoxic methylol compounds. HMM exhibits antitumor activity in alkylating agent-resistant ovarian cancer and, to a lesser extent, in several other neoplasms (lung, breast cancer, lymphomas).

HYDROXYUREA. Hydroxyurea (Hydrea, HU) acts as an inhibitor of ribonucleotide reductase, resulting in intracellular depletion of deoxynucleoside triphosphates and inhibition of DNA synthesis. It is available for clinical use in oral formulation. HU's major toxicity is to the bone marrow, and it causes transient dose-related myelosuppression. At high dosage, a megaloblastic anemia can develop, which is non-responsive to vitamin B_{12} or folic acid. Gastrointestinal side effects of nausea and vomiting are also common with high-dose therapy. HU is used primarily to treat chronic myeloid leukemia and polycythemia vera, but it also has some use in head and neck cancer and metastatic melanoma and as a radiosensitizer.

MITOXANTRONE. Mitoxantrone (Novantrone) is an anthracenedione with a structure that appears analogous to that of the anthracyclines. It has been approved by the FDA as a second-line agent for treatment of acute leukemia in relapse but is also useful in the treatment of breast cancer and lymphoma. Mitoxantrone binds to DNA and causes strand breaks and inhibits DNA and RNA synthesis. In terms of cellular response by tumor cells, there is not complete cross-reactivity between mitoxantrone and the anthracyclines. Mitoxantrone dosage for acute leukemia is higher than for solid tumors. Comparative studies in patients with advanced breast cancer suggest that it is less active and less toxic than doxorubicin. Its major acute toxicity is myelosuppression. Gastrointestinal side effects, including nausea, vomiting, and mucositis as well as alopecia, are less severe than with the anthracyclines. Mitoxantrone can cause some cardiac toxicities, usually manifest by development of arrhythmia at the time of injection, and can exacerbate pre-existing anthracycline-induced cardiomyopathy. It can be used intraperitoneally in patients with ovarian cancer, because most of the drug remains in the peritoneal cavity. This approach reduces systemic toxicity, but it can induce chemical peritonitis and adhesions.

ASPARAGINASE. L-Asparaginase (Crasnitin, Elspar) is a bacterial enzyme isolated from *Escherichia coli* or *Erwinia carotovora*. Its major use is to treat lymphoblastic leukemias and some lymphomas with a deficiency in asparagine synthetase and cellular dependence on exogenous asparagine. L-Asparagine is a non-essential amino acid, and most normal cells can synthesize their required asparagine. Therapeutically, L-asparaginase depletes the plasma of asparagine by converting it to aspartic acid and ammonia. Most patients develop fever and chills as well as nausea and vomiting after administration, but these symptoms can usually be reduced or prevented by premedication with antiemetics and anti-inflammatory agents. Asparaginase toxicity can produce abnormal liver function tests (aspartate aminotransferase T, alkaline phosphatase, and bilirubin) as well as hypoalbuminemia and reductions in plasma levels of clotting factors and insulin. Other occasional toxicities include pancreatitis and central nervous system abnormalities, which can lead to confusion or coma. Repeated use of asparaginase leads to the development of antibodies that can inhibit its activity and accelerate its clearance as well as induce hypersensitivity reactions. Patients developing hypersensitivity after asparaginase administration may exhibit hypotension, laryngeal edema, bronchospasm, and urticaria. Switching to an asparaginase derived from a different bacterial species can bypass neutralizing antibodies in hypersensitive patients. The lack of myelosuppressive or gastrointestinal toxicity has facilitated incorporation of L-asparaginase into drug combinations for the treatment of acute lymphocytic leukemia (ALL). A useful combination in ALL is methotrexate, followed 24 hours later by L-asparaginase.

MANAGEMENT OF TOXICITY

Most cytotoxic drugs are also toxic for host cells, and treatment schedules must take this into account.

DOSE ADJUSTMENTS FOR BONE MARROW TOXICITY. Doses of myelosuppressive agents often must be adjusted downward to avoid serious or life-threatening side effects such as granulocytopenic fever and thrombocytopenic bleeding. For most drugs, empirical schedules have been developed for drug administration, with single agents or combinations of myelosuppressive drugs normally given every 3 to 4 weeks. The interval between treatments provides time for hematopoietic recovery of normal myeloid progenitors in the bone marrow and avoids cumulative myelosuppression. It is essential to check the patient's white blood cell count, differential, and platelet count immediately before each course of myelosuppressive chemotherapy. During the first few cycles of chemotherapy, and at intervals thereafter, it is useful to check counts between treatment courses, particularly to determine the nadir of absolute granulocyte count (AGC). Falls of AGC below 1000/μL increase the risk of infection; AGCs below 500/μL represent a potentially fatal risk. Because hematopoietic recovery can occur rapidly after the nadir, the AGC immediately before the next course can be normal even though the nadir count may have been very low. For some drug combinations with low but brief AGC nadirs, prophylactic antibiotic agents (e.g., ciprofloxacin, sulfamethoxazole-trimethoprim) that will bracket the AGC nadir can protect against infection secondary to neutropenia. In general, if the AGC immediately before the next course of chemotherapy is less than 2000/μL, the dose of myelosuppressive drugs should be reduced by 50%. With an AGC of less than 1500/μL, doses should be reduced by 75%. If less than 1000/μL, the drug should be withheld until hematologic recovery occurs. An additional approach to problems of myelosuppression involves the use of bone marrow growth factors, as discussed below under Biologic Agents.

DOSE ADJUSTMENTS FOR IMPAIRED HEPATIC OR RENAL FUNCTION. It is important to make downward dosage adjustments for specific drugs when altered hepatic or renal function plays a major role in drug metabolism. The metabolism of doxorubicin depends on good hepatobiliary function. Patients with a serum bilirubin value of greater than 3.0 mg/dL should have their doxorubicin dose reduced by at least 50% until drug tolerance is established.

Cisplatin, methotrexate, etoposide, hydroxyurea, and bleomycin all are cleared predominantly through renal excretion. Doses of these agents should be decreased approximately in proportion to the decline in renal function as determined by creatinine clearance and reflected by the serum creatinine value.

ENDOCRINE AGENTS

Cancer cells often exhibit susceptibility to hormonal control mechanisms that regulate growth of the normal organ or tissue from which the neoplasm arose. Endocrine therapy (Table 198–9) appears generally to work through cytostatic rather than cytotoxic mechanisms and usually requires long-term suppression. Endocrine therapy includes the use of both hormones and "antihormones," which are either antagonists or partial agonists for a given endocrine mechanism. Inasmuch as the effects of hormones are receptor mediated, evaluation of receptors capable of binding hormones has played an important role in assessing both tumor types and individual patients for possible endocrine therapy.

STEROID HORMONES AND ANTIHORMONES. Cancers arising from endocrine organs and the immune system are susceptible to the effects of steroid hormones, steroid hormone antagonists, and hormone deprivation. The sex steroids and their antagonists represent major agents for the treatment of common cancers arising from the breast, prostate gland, and uterus. The role of endocrine ablation procedures (hypophysectomy, adrenalectomy, oophorectomy, orchiectomy) has diminished as systemic agents have been identified to replace surgical procedures. Nonetheless, oophorectomy and orchiectomy are still useful in the treatment of endocrine-sensitive cancers of the breast and prostate, respectively.

ESTROGENS AND ANTIESTROGENS. Pharmacologic doses of estrogen have therapeutic effects in cancers of the prostate and the breast. Orchiectomy is equally efficacious and lacks feminizing side effects. No evidence suggests an additive effect of the two.

The antiestrogen tamoxifen (Nolvadex) improves survival of postmenopausal women with estrogen and/or progesterone receptor-positive breast cancer in both the adjuvant and metastatic settings. Recent but still controversial studies also suggest that tamoxifen may be a useful adjuvant for hormone receptor–negative cancers in postmenopausal women. A recent breast cancer prevention

Table 198–9 ■ HORMONALLY ACTIVE AGENTS IN CANCER TREATMENT

REPRESENTATIVE AGENTS	DOSE (ORAL UNLESS SPECIFIED)	TOXICITY (A = ACUTE; D = DELAYED)	USES
Glucocorticoids			
Prednisone	20–100 mg/d or 50 mg qod (single dose)	A: Fluid retention, hyperglycemia, euphoria, depression, hypokalemia	Leukemia Lymphoma Myeloma
Dexamethasone	4–16 mg/d or 40 mg/d for 4-day pulses every 2–4 weeks	D: Osteoporosis, immunosuppression, gastrointestinal ulcers, cushingoid appearance, cataracts	Breast cancer Brain metastases
Estrogen			
Diethylstilbestrol	5 mg tid (breast); 1–3 mg qd (prostate)	A: Nausea, vomiting, fluid retention, hypercalcemia (flare reaction with bone metastases), uterine bleeding D: Feminization, accelerated coronary artery disease	Breast cancer Prostate cancer
Antiestrogen			
Tamoxifen	20 mg qd	A: Occasional nausea, fluid retention, hot flashes D: Retinal degeneration	Breast cancer
Toremifene			Breast cancer
Aromatase Inhibitor			
Aminoglutethimide (plus hydrocortisone 20 mg bid)	250 mg bid (breast); 250 mg qid (prostate)	A: Dizziness D: Rash (transient)	Breast cancer Prostate cancer
Anastrozole	1 mg/d	A: Nausea, vomiting	
Progestins			
Megestrol acetate Hydroxyprogesterone	40 mg qid 1 g IM biw	A: Increased appetite (megestrol), fluid retention D: Weight gain, thromboembolism	Breast cancer
Androgens			
Fluoxymesterone Testosterone	10–20 mg qd 600 mg IM q4–6 wk	A: Cholestatic jaundice (with oral drug) D: Virilization	Breast cancer
Antiandrogen			
Flutamide	250 mg tid	D: Gynecomastia	Prostate cancer
Gonadotropin-releasing hormone agonists (depot formulations)			
Leuprolide acetate Goserelin acetate	7.5 mg SQ monthly 3.6 mg SQ monthly	A: Transient flare of symptoms	Prostate cancer Breast cancer (?)

trial involving more than 1300 women at high risk for breast cancer showed that women taking tamoxifen had a lower incidence of disease than those taking a placebo. Raloxifene, also an estrogen antagonist, has been shown to reduce breast cancer risk without increasing the incidence of uterine cancer, which is a concern with tamoxifen prophylaxis. In general, cytotoxic chemotherapy rather than endocrine therapy is recommended for women with hormone-receptor–negative breast cancer. Tamoxifen is available only in 10-mg tablets for oral administration, with a manufacturer's recommended dose of 10 mg twice daily. The schedule lacks a good scientific rationale because, with chronic therapy, tamoxifen and its active metabolite dihydroxytamoxifen achieve a steady state with a large deep tissue reservoir. Accordingly, use of a single dose of 20 mg should be an acceptable alternative schedule with fewer problems with compliance. Serious or life-threatening toxicities of tamoxifen (thromboembolic disease, retinitis) are rare. Common side effects include hot flashes and weight gain, sometimes due to fluid retention. Mild nausea also may occur. In premenopausal women with hormone receptor–positive neoplasms and overt metastatic disease, both oophorectomy and antiestrogen therapy can be useful. However, cytotoxic chemotherapy remains the treatment of choice, because it appears to have curative potential. The role of ovarian ablation or antiestrogen therapy added to chemotherapy in the adjuvant setting remains to be defined. Tamoxifen has been reported as occasionally having palliative effects in other neoplasms such as ovarian or endometrial cancer. Toremiphene, an estrogen antagonist, has also been approved for the treatment of breast cancer. It appears to have similar response rates to tamoxifen in the treatment of this disease.

ANDROGENS AND ANTIANDROGENS. Androgen therapy is contraindicated in prostate cancer because it stimulates growth. Virilizing androgens such as testosterone propionate, fluoxymesterone (Halotestin), and testosterone enanthate (Delatestryl) have all been used beneficially in the treatment of metastatic breast cancer with hormone receptor–positive disease. However, androgen therapy has largely been replaced with antiestrogen therapy because the antiestrogen does not cause hirsutism, deepening of the voice, or changes in libido. Additionally, the oral halogenated androgens (e.g., fluoxymesterone) also can cause cholestatic jaundice. The antiandrogen flutamide (Eulexin) is a useful agent in the treatment of prostate cancer in combination with one of the gonadotropin-releasing hormone agonists (leuprolide, goserelin), and these combinations function as a "medical orchiectomy."

PROGESTINS. Progestins are useful in palliative management of metastatic breast or endometrial cancer and can cause tumor regression in endocrine-sensitive disease. No evidence suggests their utility in the adjuvant setting in either of these neoplasms. Occasional patients with prostate cancer also appear to benefit from progestational therapy. The most commonly used progestins include megestrol acetate (Megace), medroxyprogesterone (Provera), and hydroxyprogesterone caproate (Delalutin). Megestrol acetate is useful for second-line endocrine therapy for patients with metastatic breast cancer who initially respond to tamoxifen. In patients who experience disturbing side effects from tamoxifen (e.g., severe hot flashes), megestrol acetate may represent a reasonable alternative. In addition to its antitumor effects, megestrol acetate improves appetite in some patients with cancer-induced cachexia.

GLUCOCORTICOIDS. Adrenal steroid hormones of the glucocorticoid class (e.g., prednisone, methylprednisolone, dexamethasone) are useful in treating lymphoid malignancies and may also potentiate the effects of cytotoxic agents in these tumor types as well as in breast cancer and perhaps other neoplasms. The glucocorticoids play an important role in treating complications of cancer (hypercalcemia, cerebral edema). Glucocorticoids are lympholytic and non-myelosuppressive and have been incorporated into combination chemotherapy for acute and chronic lympholytic leukemia, malignant lymphoma, and multiple myeloma. Glucocorticoids appear to induce cell death in some lymphoid malignancies by apoptosis.

AROMATASE INHIBITORS. AMINOGLUTETHIMIDE (CYTADREN). Aminoglutethimide inhibits the first step in adrenal steroid synthe-

Additionally, and probably more importantly, aminoglutethimide also inhibits the extra-adrenal conversion of the adrenal androstenedione to estrone by the enzyme aromatase. Aromatase is found in body fat and some other tissues and explains the presence of the weak estrogen estrone in the plasma of postmenopausal women. Aminoglutethimide is useful in the palliative treatment of recurrent breast cancer in hormone receptor–positive patients. Used in combination with hydrocortisone, it suppresses endogenous steroid hormone synthesis (including androstenedione) as well as ACTH production and slows the catabolism of aminoglutethimide. Aminoglutethimide is commonly administered in a dose of 250 mg twice daily along with 20 mg of hydrocortisone. Somewhat higher doses have been employed for second-line endocrine therapy for metastatic prostate cancer. Patients receiving aminoglutethimide and hydrocortisone should be cautioned against abrupt cessation of therapy to avoid symptoms of adrenal insufficiency.

ANASTROZOLE. Anastrozole (Arimidex) is a selective non-steroidal aromatase inhibitor. Unlike aminoglutethimide, which is neither selective nor a powerful aromatase inhibitor, anastrozole is the first orally administered aromatase inhibitor approved by the FDA for the treatment of postmenopausal women with advanced breast cancer. The drug has an excellent toxicity profile, and only a small percentage of patients who receive a 1-mg/day dose experience nausea, asthenia, headache, or hot flashes.

GONADOTROPIN-RELEASING HORMONE (GnRH, LHRH) AGONISTS. Several synthetic analogues of natural GnRH (LHRH) are now clinically available. Both leuprolide acetate (Lupron) and goserelin acetate (Zoladex) are available in long-acting parenteral-depot formulations. These analogues function more potently than natural GnRH agonists and also have an unusual effect on the pituitary, consisting of initial stimulation followed by long-term inhibition of release of follicle-stimulating hormone and leuteinizing hormone. This initial increase in gonadotropins can cause a transient increase in symptoms in patients with bone metastases. The inhibition of release of the gonadotropin reduces testicular androgen synthesis in men and ovarian estrogen production in women. Accordingly, GnRH offers an alternative to surgical orchiectomy in patients with prostate cancer and avoids the gynecomastia, nausea, vomiting, edema, and thromboembolic disease that estrogens may produce. The effectiveness of GnRH agonists is enhanced by administration in combination with an antiandrogen (flutamide), and the combination has been reported to be more effective than a GnRH agonist alone in patients with stage D metastatic prostate cancer. Potence results from this form of "medical orchiectomy," as it does from surgical orchiectomy, but the effects of medical therapy are potentially reversible if treatment is discontinued. Medical orchiectomy is more expensive but acceptable to patients who decline surgical orchiectomy. GnRH agonists now show promise in combination with antiestrogens as endocrine therapy for premenopausal women with hormone receptor–positive breast cancer. The GnRH agonists are abortifacients in animals and should not be given to women who are or may become pregnant.

BIOLOGIC THERAPY

A new form of cancer therapy, still in its evolution, is the use of recombinant cytokines, vaccine growth factors, and monoclonal antibodies for the treatment of cancer (Table 198–10). The term *biologic therapy* describes this heterogeneous group of agents that alter or are normal mammalian mediators or achieve antitumor effects through endogenous host defense mechanisms. The biologic agents have also been termed *biologic response modifiers*. Both the cellular and humoral limbs of immunity can be exploited in cancer therapy. The cellular defenses include several classes of cytotoxic leukocytes (natural killer cells), lymphokine-activated killer (LAK) cells, tumor infiltrating lymphoma, and cytotoxic T lymphocytes, as well as antibody-dependent cytotoxic cells. The non-specific cells of the reticuloendothelial system, including activated macrophages, also may be important. Humoral agents with antitumor activities include cytokines such as interferons and interleukins as well as specific antibodies. Most of these humoral agents interact with specific immune effector cells in a coordinated and synergistic fashion. The general availability of cytokines and growth factors has been facilitated by the development of recombinant DNA technology. Antibodies are highly specific and generally interact directly with their tumor targets when they are targeted against cell-surface constituents. Some humoral agents, including the tumor necrosis factors-α and -β, have demonstrated potent local antitumor properties in preclinical models but have yet to be shown to be clinically useful.

Table 198–10 ■ BIOLOGIC THERAPY OF CANCER: APPROACHES AND AGENTS

APPROACH	AGENTS
Active immunotherapy	
Non-specific	Adjuvants: BCG, levamisole Cytokines: Interferons, interleukin-2
Specific	Tumor cell vaccines
Passive serotherapy	
Antibodies	Polyclonal or monoclonal antibodies (alone or conjugated with drugs, radionuclides, or toxins)
Adoptive cellular therapy	Lymphokine-activated killer cells Tumor-infiltrating lymphocytes
Immunomodulators	Levamisole, thymic hormones
Bone marrow growth factors	G-CSF, GM-CSF, M-CSF, interleukin-3, erythropoietin
Growth factor antagonists	Suramin Antibodies to growth factor receptors (e.g., epidermal growth factor, HER-2/neu, interleukin-2 receptors)
Antiangiogenesis agents	Endostatin Angiostatin

G-CSF, GM-CSF, and M-CSF = granulocyte, granulocyte-macrophage, and macrophage colony-stimulating factors.

Vaccines based on specific bacterial agents or extracts from bacteria can non-specifically activate the host immune system. By using BCG, this approach has been applied successfully to intravesical therapy of in situ cancer of the urinary bladder. Specific cancer-associated antigen vaccines are under active investigation.

INTERFERONS. The interferons (IFNs) are a family of antiviral proteins that differ in their cellular origin and polypeptide structure as well as in their clinical applications. The three major molecular species are IFN-α, -β, and -γ. IFN-α and -β mediate their action by binding to the same cell surface receptor, whereas a second cell-surface receptor mediates the action of IFN-γ. IFN-α is the major species for use in the treatment of hematologic malignancies and solid tumors. Whether IFN-β or -γ will have sufficient advantage over IFN-α in any specific cancer indication to gain regulatory approval is uncertain.

INTERFERON-α. Recombinant IFN-α (IFN-α_2, Intron-A, Roferon-A), a polypeptide cytokine with antiviral properties, is useful for single-agent treatment of selected hematologic malignancies and solid tumors. The precise mechanism of action of IFN is still poorly understood, but it is known to activate the transcription of a number of cellular genes. Additionally, IFN inhibits the synthesis of a number of proteins in sensitive tumor target cells, including ornithine decarboxylase, a rate-limiting enzyme in polyamine metabolism. Although IFN-α also has antiviral and immunoregulatory properties that alter the biologic function of many cell types involved in humoral and cellular immunity, it is unclear whether these functions influence its antitumor properties above and beyond its direct receptor-mediated effects on sensitive tumor cells. The antitumor properties of IFN-α also appear to be schedule dependent with a cytostatic mode of action. Most remissions induced by IFN are only partial.

IFN-α can be administered parenterally by intravenous, intramuscular, subcutaneous, and intracavitary routes. Its preferred route is by subcutaneous administration, which provides the longest duration of action. The dosage schedules are quite variable, with higher dosages required for some tumor types. Hairy cell leukemia is the tumor most sensitive to IFN-α. Usual dosages are in the range of 3 million IU administered subcutaneously three times weekly. At these low levels, IFN usually causes only mild side effects such as fever and chills with the first few doses. For Kaposi's sarcoma, far more aggressive and toxic IFN schedules are required and can cause anorexia, weight loss, failure in concentration, and profound weakness. High-dose IFN can also induce occasional cardiac arrhythmias, nausea, vomiting, leukopenia, myalgias, proteinuria, and

hepatic dysfunction. Elderly patients appear to develop more marked side effects at all dosage schedules.

IFN-α is also useful in the treatment of chronic myeloid leukemia, multiple myeloma, some of the low-grade non-Hodgkin's lymphomas, and in some patients with metastatic melanoma or renal cell carcinoma. In melanoma, the use of high doses of IFN-α in an adjuvant mode has been shown to decrease the relapse rate. In myeloma, IFN-α appears to lengthen remissions induced by chemotherapy. Patients receiving recombinant IFN-α for hairy cell leukemia, CML, or renal cancer have developed neutralizing antibodies to the recombinant product when the disease progresses again after an IFN-induced remission. A limited number of patients using neutralizing antibodies have been successfully re-treated by switching to non-recombinant IFN-α. IFN-α has been incorporated into combination therapy with various cytotoxic and endocrine agents. At present, use of IFN-α in combination with 5-FU is being explored in combination with *cis*-retinoic acid to treat renal and cervical cancers. Although the clinical indications for IFN therapy continue to grow gradually, it has lacked the type of broad-spectrum anticancer effects that were initially envisioned.

INTERLEUKIN-2. Interleukin-2 (IL-2, Proleukin) is an immunomodulatory cytokine that acts on T-cell progenitors to produce LAK cells. Recombinant IL-2 has been approved for therapeutic use in renal cancer. Direct intravenous infusion induces LAK cells in the patient. Additionally, leukapheresis can obtain circulating lymphocytes that can then be exposed to IL-2 in tissue culture to activate lymphoid progenitors into LAK cells, which are then reinfused into the patient. There is now general agreement that either IL-2 or IL-2/LAK can induce tumor regression in 10 to 20% of patients with renal carcinoma or melanoma.

Whereas the infusion of LAK cells causes relatively few side effects, IL-2 induces considerable toxicity. Patients receiving high-dose IL-2 must be in an intensive-care unit with close management of blood pressure, fluids, and electrolytes. The high-dose regimens are suitable only for younger patients without other significant disease or impairment of cardiac, pulmonary, hepatic, or renal function. Common side effects of high-dose IL-2/LAK are probably due to lymphoid infiltrates in major organs and an induced capillary leak syndrome. Shortly after initiation of high-dose IL-2 therapy, tachycardia develops, and a significant drop in arterial blood pressure occurs. As IL-2 administration continues, compensatory fluid retention occurs in association with weight gain, oliguria, and azotemia. Vasopressors are often needed. Even at lower doses that can be used in a conventional hospital or outpatient setting (e.g., 3 million IU/m^2/day by intravenous infusion for 2 weeks), hypotension and fluid retention are not uncommon.

Pulmonary metastases appear to be somewhat more sensitive to IL-2 or IL-2/LAK therapy than are other tumors. With the adoptive immunotherapy approach using IL-2/LAK, a small percentage of patients who had undergone prior removal of the primary tumor achieved complete remission, with all evidence of metastatic disease disappearing for prolonged periods of time. Some controversy nonetheless remains as to whether the use of high-dose IL-2/LAK has any advantage over administration of IL-2 alone at a lower and better-tolerated dosage level.

LEVAMISOLE. Levamisole (Ergamisole) is an anthelmintic agent possessing immunopotentiating properties. It has been reported to enhance various tests of cell-mediated immunity in patients with Hodgkin's disease but has not been shown to have a therapeutic effect. When combined with 5-FU, however, levamisole has been reported to enhance adjuvant chemotherapy of patients with Dukes' C colon cancer, although this regimen has been largely supplanted by treatment with 5-FU and leucovorin. In patients with overt metastatic colon cancer, the combination of 5-FU and levamisole does not appear to be any more useful than 5-FU alone.

ANTITUMOR ANTIBODY THERAPY

RITUXIMAB. Rituximab (Rituxan) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD-20 antigen found on the surface of normal and malignant B-lymphocytes. It is the first antibody approved for therapeutic use in humans. Approximately 50% of patients with relapsed or refractory low-grade lymphoma treated with 375 mg/m^2 of this agent given as an IV infusion weekly for four doses had a partial or complete remission lasting 10 to 12 months. Current studies are exploring the use of this antibody together with chemotherapy and/or irradiation. Use of this antibody to deliver radioactivity to lymphoma tumor sites is also under investigation. Infusion-related side effects consisting of fever, chills, and rigors occur in the majority of patients during the first infusion. Subsequent infusions are associated with fewer side effects.

TRASTUZUMAB (HERCEPTIN). This genetically engineered monoclonal antibody is directed against cells overexpressing the HER-2 protein, a transmembrane glycoprotein. Approximately 30% of breast cancers overexpress this protein. The response rate to the antibody alone in this group of patients is low (about 15%); however, in combination with taxol or doxorubicin, augmented response rates have been reported, leading to the approval of this antibody for clinical use by the FDA. An unexpected side effect of this treatment has been an increased incidence of cardiac toxicity when this antibody is used in combination with doxorubicin or taxol.

GROWTH FACTOR ANTAGONISTS. The use of antagonists to polypeptide growth factors is an extension of neuroendocrine therapy but represents a form of biologic therapy as well. One growth factor antagonist that has been recognized to have anticancer properties is suramin, which has been used since the 1920s for the treatment of African sleeping sickness. Suramin is a polysulfonated napthylurea that binds tightly to heparin-binding growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF-1). Exclusion of growth factors from their receptors can result in "programmed cell death." Suramin actively treats prostate cancer, presumably by blocking the action of FGF and other growth factors. Suramin also inhibits the function of a variety of enzymes and other proteins, so its precise mechanism of antitumor action remains to be defined. Suramin's multiple actions also account for a broad range of toxicities, which can be severe or irreversible. One of these is adrenal insufficiency, which requires long-term adrenal steroid replacement. Frequent plasma monitoring of suramin concentrations is essential, because there is the potential for serious neuropathy when suramin concentrations exceed 300 mg/mL. Suramin represents the first member of a new class of investigational agents for cancer therapy. Another approach to growth factor receptor blockade involves use of monoclonal antibodies to epidermal growth factor (EGF) receptor and the IL-2 receptor.

BONE MARROW GROWTH FACTORS (See Chapter 158). A new approach to supportive care for bone marrow failure associated with cancer and for maintaining adequate hematopoietic function between courses of myelosuppressive chemotherapy is to administer bone marrow growth factors to stimulate an increased rate of production of myeloid progenitors (Table 198–11). The bone marrow growth factors are glycoproteins that function in an overlapping and hierarchic manner on bone marrow progenitors and not only result in cell proliferation but also activate differentiation and cell trafficking. The major factors also potently stimulate the proliferation of myeloid precursors. Several of these recombinant proteins, including granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and erythropoietin (Epogen, EPO), are widely used in cancer treatment. IL-3, macrophage colony-stimulating factor (M-CSF), and thrombopoietin are at an earlier stage of development, and their role in supportive care is currently uncertain. Clinical trials using subcutaneously administered G-CSF or GM-CSF have shown that either can shorten the duration of granulocytopenia, the frequency of

Table 198–11 ■ RECOMBINANT BONE MARROW GROWTH FACTORS OF POTENTIAL IMPORTANCE IN SUPPORTIVE CARE OF CANCER PATIENTS

GROWTH FACTOR	EFFECTS
G-CSF	Stimulates granulocyte production
GM-CSF	Stimulates granulocyte, macrophage, and eosinophil production
M-CSF	Stimulates macrophage production and activation
Interleukin-3	Stimulates granulocyte, macrophage, and platelet production
Erythropoietin	Stimulates production of red blood cells
Interleukin-11	Stimulates platelet production
Thrombopoietin	Stimulates platelet production

G-CSF, GM-CSF, M-CSF = granulocyte, granulocyte-macrophage, and macrophage colony-stimulating factors.

infectious complications, and the duration of hospitalization after chemotherapy combinations that normally require inpatient administration. With bone marrow transplantation, in which high-dose chemotherapy and/or total body radiation is used, both myelosuppressive and nonmyelosuppressive side effects can be diminished with the use of G-CSF or GM-CSF. Preliminary evidence suggests that IL-3 (multi-CSF) can stimulate platelet and red blood cell as well as granulocyte production.

In preclinical studies, IL-3 also appears to act synergistically with GM-CSF to produce more complete and rapid recovery of circulating granulocytes and platelets. The major toxicities of the growth factors that stimulate white blood cell production include fever, myalgias, and occasional rashes. Pericarditis has been reported with high-dose GM-CSF or G-CSF. Recombinant EPO is already in general clinical use for the anemia of renal failure. Preliminary studies also suggest that when used in pharmacologic doses, EPO can restore normal red blood cell counts in some patients with multiple myeloma and perhaps in some other hematologic malignancies as well. EPO also has promise for reducing the degree of anemia induced by cytotoxic chemotherapy.

DIFFERENTIATION THERAPY. All-*trans*-retinoic acid is the first effective differentiation agent introduced into routine clinical care. It causes a high percentage of complete remissions in patients with acute promyelocytic leukemia. Retinoids are also under investigation as chemotherapeutic and chemopreventive agents.

ANTIANGIOGENESIS TREATMENTS. An attractive target for anticancer drug development is the neovasculature elicited by growth of tumors. Natural substances derived from precursor proteins (e.g., endostatin, a 20 kd-terminal fragment of collagen, and angiostatin, a 38-kd internal fragment of plasminogen), show encouraging antitumor effects in animal models. These studies have also stimulated a search for natural products as well as new synthetic agents with the goal of generating small molecule inhibitors of tumor cell vasculature. This approach may provide relatively non-toxic treatment of tumor cell growth because tumor-derived endothelial cells proliferate rapidly but normal endothelial cells usually do not replicate.

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Holland JF, Frei E III, Bast RC Jr, et al: Cancer Medicine, 4th ed. Philadelphia, Lea & Febiger, 1997. *A comprehensive textbook covering clinical, diagnostic, and therapeutic approaches for all major forms of cancer. Major modalities of treatment as well as drug combination schedules are delineated in detail in relation to relevant tumor types.*

199 ONCOLOGIC EMERGENCIES

Stephen M. Hahn

The clinical course of patients with cancer is characterized by the development of complications from either the underlying malignancy or from therapy. To avoid significant morbidity and mortality, the clinician must be aware of the signs and symptoms of these complications and perform a rapid evaluation followed by the appropriate institution of treatment. Several types of cancer are now routinely cured; and for others, treatment brings an increase in the patient's quality of life and survival time. Therefore, the early recognition and treatment of oncologic emergencies has an important role in the medical management of cancer patients.

FEVER AND NEUTROPENIA. One of the most common oncologic emergencies is fever (a single temperature of 38.5° C [101.3° F] or three temperatures of 38° C [100.4° F] within a 24-hour period) and neutropenia (absolute neutrophil count less than 1000/mm³). Neutropenic cancer patients have an increased risk of systemic infection and may rapidly develop sepsis (see Chapter 96). Emergent empiric antibiotic therapy is crucial.

The risk of infection increases once the neutrophil count drops below 1000/mm³. Disruptions of other host defenses will also predispose to infection. Paramount among these is breakdown of the gastrointestinal barrier with mucositis. Additional factors include indwelling catheters, invasive procedures, and abnormal cellular and humoral immunity.

The febrile, neutropenic patient usually presents with few signs or symptoms other than fever. Localized infection may be present but not clinically apparent. The absence of an adequate number of leukocytes may make the detection of an active infection difficult. A careful history and physical examination must be performed, focusing on common sites of infection. The oral cavity should be inspected for evidence of mucositis and lesions suggestive of anaerobic, viral (especially *Herpes simplex*), and fungal (especially *Candida* species) infection. Examination of soft tissue and skin, especially at catheter sites, may show early cellulitis or septic phlebitis. A perirectal abscess should be excluded by careful palpation of the anorectal area for induration, fluctuance, or tenderness.

Before initiation of antibiotic therapy, cultures should be performed on all patients and sent routinely for isolation of bacteria and fungi. Blood cultures must be obtained both from the port of an indwelling central catheter and from peripheral veins. If an indwelling catheter is suspected to be the source of infection, removal of the catheter is not always required but must be considered. If the catheter is removed, the tip should be sent for Gram stain and culture. Sputum examination by Gram stain and culture are usually not helpful but are obtained if sputum is produced. Gram stain as well as bacterial, fungal, and viral cultures should be ordered for all oral, skin, and soft tissue lesions. Biopsies of cutaneous lesions may be especially helpful in the diagnosis of systemic viral and fungal infections and can be safely performed in the neutropenic patient. A chest radiograph, urinalysis with microscopy and culture, and evaluation of ascites and pleural fluid should be performed. Although meningitis is not typically encountered in febrile neutropenic cancer patients, a lumbar puncture should be performed when suggestive clinical signs or symptoms exist.

Use of indwelling urinary tract catheters and unnecessary intravenous catheters is to be avoided. Strict hand washing by all hospital personnel is required. Aggressive prophylactic or therapeutic mouth care (suggested regimen: nystatin suspension, diphenhydramine [Benadryl]/antacid/lidocaine mixture, and 5% sodium bicarbonate solution, alternating each every 2 hours, administered as swish and spit) will provide relief of symptoms and may improve the patient's course.

Once evaluated and hospitalized, the patient should be started without delay on broad-spectrum antibiotics that include coverage for *Pseudomonas* species and other gram-negative organisms. Recently there has been a shift toward gram-positive organisms as the cause of infection in the neutropenic patient. Therefore, antibiotic regimens with broad coverage are required. Many antibiotic regimens have been evaluated in prospective studies, and there is no clearly superior regimen. Emerging antimicrobial resistance at an individual institution may dictate the antibiotics administered to the neutropenic patient. Suggested regimens are (1) monotherapy with a third- or fourth-generation cephalosporin (cefepime, 2 g every 12 hours, or ceftazidime, 1 to 2 g every 8 hours intravenously), (2) a semisynthetic penicillin (piperacillin, 3 to 4 g every 4 hours intravenously) plus an aminoglycoside (gentamicin or tobramycin, 2 mg/kg loading dose followed by one to three divided doses daily depending on renal function), or monotherapy with imipenem (50 mg/kg divided every 6 hours intravenously). If a specific organism is suspected, appropriate antibiotics should be added to the initial regimen. For example, if infection of an indwelling catheter is likely, additional gram-positive coverage with vancomycin (500 mg every 6 hours intravenously) should be added to cover infection with *Staphylococcus aureus* and *Staphylococcus epidermidis*. For patients with mucositis, periodontal infections, or perianal infections, anaerobic coverage with either metronidazole (15 mg/kg loading dose intravenously and 7.5 mg/kg intravenously every 6 hours) or clindamycin (300 mg intravenously every 6 hours) should be started while awaiting culture results. Antifungal agents such as fluconazole should be given to patients who present with suspected oral thrush or esophagitis, but these agents do not replace amphotericin B in the treatment of documented or suspected invasive fungal infections. Fluconazole prophylaxis to prevent invasive mycotic infections is of unknown benefit and is not routinely recommended at this time.

If fever persists after the initiation of antibiotics, cultures and diagnostic studies should be repeated and the spectrum of antibiotic coverage should be broadened. Patients with prolonged neutropenia who are receiving broad-spectrum antibiotics are at high risk for